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Reproductive-Aged Adults Diagnosed with Tuberous Sclerosis Complex (TSC): Understanding of Clinical Variability, Perceived Disease Burden, and Reproductive Decision-Making

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REPRODUCTIVE-AGED ADULTS DIAGNOSED WITH TUBEROUS SCLEROSIS COMPLEX (TSC): UNDERSTANDING OF CLINICAL VARIABILITY, PERCEIVED DISEASE BURDEN, AND REPRODUCTIVE DECISION-MAKING

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Dedication

For Mel who has been my unwavering support.

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Abstract

Tuberous Sclerosis Complex (TSC) is a highly variable autosomal dominant multisystem disorder characterized by the growth of benign tumors, epilepsy, and TSC-associated neuropsychiatric disorders (TAND). There is a high level of clinical variability, even within the same family. While reproductive decisions always carry a level of uncertainty, individuals with highly variable genetic conditions like TSC must consider both the chance of passing on the condition and the uncertain clinical presentation. There is currently no literature on factors influencing reproductive decisions of adults with TSC. To address this gap in understanding, we conducted an exploratory mixed-methods survey utilizing an anonymous online questionnaire to assess study participants': 1) familiarity with the symptoms of TSC, 2) understanding of the risk of passing on TSC, 3) perceived disease burden/quality of life, and 4) family planning considerations. A total of 175 individuals aged 18-45 who were diagnosed with TSC were included in the final data set. Participants were highly familiar with symptoms of TSC with an average symptom knowledge score of 86.64%. Cortical tubers, angiofibromas, angiomyolipomas, and seizures were recognized as symptoms of TSC by more than 95% of participants. Lymphangioleiomyomatosis (LAM) was the least recognized symptom (75.29%), with females being statistically more likely to recognize the symptom than males. Most participants (85.96%) were aware of the 50% recurrence risk of TSC. Perceived disease burden was low with 58.58% viewing themselves as mildly or very mildly affected. Our

disease burden/quality of life instrument found that a majority of participants reported that they felt different from those around them, that they were frustrated by their symptoms, that their symptoms made them anxious, and that they thought about their TSC at least some of the time. Sleep disturbance and pain caused by TSC were also common. However, a majority of participants felt like they were in control of their lives, felt good about their social life, felt comfortable meeting new people, and felt they had the support they needed. Around 60% of our study population was considering having future children with the average desired number of children equaling 2.25. Reproductive methods being considered included traditional conception (52.94%), adoption (45.10%), donor gametes or embryos (17.64%), and preimplantation genetic diagnosis ([PGD], 50.00%). Thematic analysis showed desire for biological children, personal health, desire to not pass on TSC, financial concerns, and fertility issues were major factors in choice of reproductive method. Interest in prenatal testing was high with 67.44% stating they would test a hypothetical future pregnancy. Thematic analysis showed being informed, considering termination of pregnancy, and accepting whatever happens as major themes for individuals' interest or lack thereof in prenatal testing. While more studies are needed, the results of this survey will help genetic counselors address reproductive concerns of clients with TSC. In particular, this study points to education gaps in TSC clinical symptoms and the underlying genetics which should be addressed by genetic counselors and other health professionals who are counseling adults with TSC.

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List of Abbreviations

AML ..... Angiomyolipoma

LAM ..... Lymphangioleiomyomatosis

mTOR..... Mammalian Target of Rapamycin

NMI..... No Mutation Identified

PGD ..... Preimplantation Genetic Diagnosis

SEGA..... Subependymal Giant Cell Astrocytoma

SEN ..... Subependymal Nodule

TAND ..... TSC-Associated Neuropsychiatric Disorders

TSC..... Tuberous Sclerosis Complex

VUS..... Variant of Uncertain Significance

CHAPTER 1

Literature Review

Tuberous Sclerosis Complex

Tuberous Sclerosis Complex (TSC) is a multisystem disorder characterized by the growth of hamartomas (benign tumors) in the skin, brain, heart, lungs, kidneys, and eyes (Islam & Roach, 2015). Abnormalities in the brain can result in neurological and psychological manifestations including epilepsy, intellectual disability, and autism (Capal et al., 2017; Prather & de Vries, 2004). Current estimates suggest that TSC affects between 1 in 6,000 to 1 in 10,000 births across all ethnicities (Northrup & Krueger, 2013). TSC is caused by an autosomal dominant mutation in one of two genes: *TSC1* which encodes the protein hamartin, and *TSC2* which encodes the protein tuberin (Nellist et al., 1993; vanSlegtenhorst et al., 1997). Hamartin and tuberin bind to form a protein complex which regulates cell growth, size, and proliferation through the mammalian target of rapamycin (mTOR) pathway (Caban, Khan, Hasbani, & Crino, 2017). Mutations in either gene can result in the protein complex failing to inhibit mTOR activity resulting in hyperactivation and uncontrolled cell growth and proliferation (Caban et al., 2017). Current genetic testing methods can identify a pathogenic variant in 75 to 90% of individuals, with two-thirds possessing a *TSC2* pathogenic variant while the remaining third possess a *TSC1* pathogenic variant (Peron, Au, & Northrup, 2018). While some symptoms (i.e., intellectual disability, autism spectrum disorder, etc.) are seen more frequently in individuals with *TSC2* pathogenic variants, there is little genotype-phenotype correlation and individuals within the same family can vary from mildly to severely affected (Caban et al., 2017; Dabora et al., 2001; Peron et al., 2018). The

phenotype depends on the age of the patient, the number and size of lesions, the organs involved, and the exact location of the lesions (Whittemore, Sampson, & Gomez, 1999).

Physical Manifestations

While lesions can occur anywhere in the body, the skin and the brain are the most commonly affected organs with lesions occurring in more than 90% of individuals (Wataya-Kaneda et al., 2017). Possible skin lesions include hypomelanotic macules or "ash leaf spots," confetti lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques, and periungual fibromas (Northrup & Krueger, 2013). Brain structure abnormalities include cortical tubers, white matter radial migration lines, subependymal nodules (SEN), and subependymal giant cell astrocytomas (SEGA) (Northrup & Krueger, 2013). Benign tumors may also grow in the heart (i.e., rhabdomyomas), kidney (i.e., angiomyolipomas), and eyes (i.e., retinal hamartomas) (Northrup & Krueger, 2013).

While the tumors associated with TSC are typically benign, they nonetheless have significant impact on morbidity and mortality (Amin, Lux, Calder, et al., 2017). One major health concern is kidney damage and possible renal failure resulting from angiomyolipomas, cysts, or in rare cases renal cell carcinomas, particularly in individuals over the age of 30 (Rentz et al., 2018). Some individuals with TSC may also have features of polycystic kidney disease due the proximity of the *PKD1* gene to the *TSC2* gene on chromosome 16 (Caban et al., 2017). Individuals with large mutations in this region typically have earlier onset and more severe kidney disease than seen in typical TSC cases. Around 30% of women with TSC develop lymphangioleiomyomatosis (LAM), a lung disorder characterized by overgrowth of smooth muscle and replacement of the

parenchyma with cysts resulting in progressive loss of respiratory function, possible pneumothorax, and eventual respiratory failure (Frost & Hulbert, 2015). It is believed that LAM predominantly affects females because LAM lesions express estrogen and progesterone receptors (Berger, Khaghani, Pomerance, Yacoub, & Coombes, 1990).

Neurological Manifestations

In addition to the growth of benign tumors, individuals with neurological involvement may experience epilepsy and TSC-associated neuropsychiatric disorders (TAND) including developmental delay, intellectual disability, autism spectrum disorder, and behavioral disturbances (Curatolo, Moavero, & de Vries, 2015). Seizures affect approximately 72 to 85% of individuals with TSC and persist regardless of treatment in roughly 60% of cases (Chu-Shore, Major, Camposano, Muzykewicz, & Thiele, 2010; Curatolo et al., 2015). Early-onset or uncontrolled seizures, particularly infantile spasms, are associated with developmental delay, intellectual deficits, and behavioral disorders (Capal et al., 2017; F. E. Jansen et al., 2008; Kopp, Muzykewicz, Staley, Thiele, & Pulsifer, 2008; Numis et al., 2011; Winterkorn, Pulsifer, & Thiele, 2007). Approximately half of children with TSC have intellectual disability ranging from borderline to profound (de Vries et al., 2018; Winterkorn et al., 2007). In children with normal intellectual ability, between 30% and 60% will experience learning difficulty in reading, writing, spelling, and mathematics (Curatolo et al., 2015; de Vries et al., 2018). Behavioral disturbances are common with around 40 to 50% of children diagnosed with autism spectrum disorder, and around 50% diagnosed with attention deficit hyperactivity disorder (Curatolo et al., 2015). Individuals can also exhibit aggressive outbursts, impulsivity, overactivity, temper

tantrums, sleep difficulties, mood swings, anxiety, and self-injury (Prather & de Vries, 2004). The Tuberous Sclerosis Registry to Increase Disease Awareness (TOSCA) natural history study found that the most common behavioral problems were overactivity (45%), sleep difficulties (43.9%), impulsivity (42.7%), anxiety (33.3%), mood swings (29.8%) and depressed mood (19.2%) (de Vries et al., 2018). The rates and types of TAND also vary by age with a larger proportion of adults experiencing anxiety (50.9%), depressed mood (43.9%), and mood swings (40.8%) (de Vries et al., 2018). TAND are some of the most difficult symptoms for families to manage and parents often report significant stress due to their child's intellectual deficits and behavioral problems (Kopp et al., 2008).

Variable Expression

As an autosomal dominant condition with nearly full penetrance, individuals with TSC have a 50% chance of passing on their condition to each of their children. While the genotypic risk is clear, the phenotypic risk is less certain. In some individuals, the condition is so mild that it is only diagnosed when a more severely affected family member is born (Caylor et al., 2018; Fox et al., 2017; Robyr, Bernard, Roume, & Ville, 2006). This high level of phenotypic variability poses a challenge when affected individuals are faced with family planning decisions since it is impossible to predict the degree to which a child may be affected. TSC also has a relatively high *de novo* mutation rate with around two out of three cases occurring in individuals with no family history (Caban et al., 2017). Due to the rarity of the condition, individuals with *de novo* mutations may have no exposure to the phenotypic range of TSC outside their own experience. While reproductive decisions always carry a level of uncertainty, individuals with highly

variable genetic conditions like TSC must first contend with the chance of passing on the condition, and then with the uncertain clinical expression. Studies on reproductive decision making have shown that the actual calculated genetic risk interacts with the perceived burden of the condition to determine an individual's reproductive choices (Hallowell & Richards, 1997). Thus, perceived quality of life would likely be a major factor in the reproductive decisions of individuals with TSC.

Quality of Life with TSC

Jansen et al. (2017) recently presented the results of a survey assessing quality of life in 111 patients including 45 adults with TSC. They found that 55.6% of adults with TSC reported that their career, education, and interpersonal relationships outside the family had been adversely affected by TSC. Nearly half (48.6%) reported anxiety or depression, and 40% reported significant pain or discomfort. These preliminary findings suggest that TSC has a substantial impact on individuals' health and wellbeing. While there are currently no studies assessing the impact of quality of life on reproductive decisions in TSC patients, the findings of Jansen et al. suggest that a higher perceived disease burden may negatively impact reproductive decisions.

Reproductive Decisions in Variable Genetic Conditions

While reproductive decisions of individuals with TSC have yet to have been studied, research into other dominant conditions with variable expressivity can provide insights into how individuals with TSC may approach reproductive decisions. For example, one study found that 62% of individuals diagnosed with Marfan syndrome (a connective tissue disorder affecting the bones, skin, eyes, and cardiovascular system) felt the

condition significantly influenced reproductive decision-making (Peters, Kong, Hanslo, & Biesecker, 2002). This was particularly true for individuals with a family history or those who were diagnosed before the age of fifteen. The influence of Marfan syndrome on reproductive decision-making correlated with the perception that Marfan syndrome had significant negative consequences on the affected individual's life (Peters et al., 2002). Additionally, individuals with a family history and therefore presumably more exposure to possible negative consequences of the condition were less likely to have children than those without a family history (Peters et al., 2002).

A study on individuals affected by Neurofibromatosis 1 (NF1) had similar findings with participants stating that the variability of the condition was a major complicating factor in family planning (Benjamin et al., 1993). Like TSC, NF1 is characterized by patches of skin pigment variation and the growth of benign skin tumors which can range from mild cosmetic differences to severe disfigurement. Affected individuals may also experience learning difficulties (30% of cases) and epilepsy (4% of cases). Benjamin et al. (1993) found that a majority of their study respondents perceived themselves as more severely affected than medical classification would suggest, particularly those who were concerned about the cosmetic aspects of the condition. NF1 posed a significant burden for many respondents with 63% reporting difficulty in school, 48% reporting anxiety during adolescence due to cosmetic symptoms, and 17% reporting teasing. In a similar study, severely affected individuals reported that they did not see themselves as likely to get married due to their condition, indicating that NF1 had a negative influence on their quality of life (Ponder et al., 1998). When asked about hypothetical children, half of

severely affected individuals reported that they would not want to have children with NF1 (Ponder et al., 1998). The study also found that affected parents who had more severely affected children reported feelings of distress and guilt for having known the risk of passing on NF1 without fully understanding the chance of increased severity in their child (Ponder et al., 1998).

Stigmatization

As seen in the studies on NF1, one major aspect of quality of life for individuals with visible differences is actual or perceived stigmatization. This is particularly true for individuals with facial differences. A recent study on individuals with facial port wine stain found a moderate negative influence on quality of life, particularly emotional wellbeing (Hagen, Grey, Korta, & Kelly, 2017). Participants reported depression (26.2%) and anxiety (33.6%) due to their facial differences, with women having more emotional effects. Other studies on children and teenagers with port wine stain showed increased rates of bullying, teasing, and social isolation (Vivar & Kruse, 2018). For individuals with TSC, growth of angiofibromas may lead to facial disfigurement which can negatively impact quality of life (Crall et al., 2016). While treatment with topical sirolimus ointment can greatly improve the appearance of angiofibromas and have a positive impact on quality of life (Amin, Lux, Khan, & O'Callaghan, 2017), this treatment has only been available since 2010 (Haemel, O'Brian, & Teng, 2010). Therefore, many adults with TSC likely grew up with stigmatization for their facial difference that may have had a negative impact on their self-esteem and quality of life. When thinking about their future children, adults with TSC

will likely remember these past experiences and possibly imagine a similar situation for their children.

Prenatal Testing and Selective Reproduction

While perceived quality of life appears to greatly affect reproductive decisions of individuals with dominant genetic conditions, interest in prenatal testing varies. For NF1, greater exposure to the condition appears to lessen the likelihood of expressing interest in prenatal testing. A recent study of pregnant women with NF1 referred to an obstetrics center in Italy found that 90% of women with a family history of NF1 were not interested in prenatal testing while 83% of those with no family history were interested in prenatal testing (Cesaretti et al., 2013). Benjamin et al. (1993) found that 12 out of 29 respondents considering future children would be interested in prenatal diagnosis of NF1, and of those, three would consider termination of the pregnancy if affected. While Benjamin et al. did not report whether respondents interested in prenatal testing had a family history of NF1, the authors noted that those who stated they would consider termination rated their own symptoms or their family member's symptoms of NF1 as moderate. This result suggests that individuals considering termination may have less exposure to individuals with severe symptoms who are nonetheless living a quality life. In the case of Marfan Syndrome, a majority (69%) of study participants expressed interest in prenatal diagnosis, though the study did not address whether the interest was for increased knowledge during pregnancy or with the intention to selectively terminate (Peters et al., 2002). The study also did not address whether those expressing interest in prenatal testing had a family history of Marfan Syndrome or the severity of their symptoms.

While interest in prenatal diagnosis does not necessarily equate to interest in termination of affected pregnancies, people often conflate the two concepts. Therefore, when asking study participants about their reproductive decisions and interest in prenatal testing it is important to recognize that participants may interpret the question as interest in selecting against an affected child either by using alternative reproductive methods or terminating affected pregnancies. A recent study of adults with physically or cognitively impairing genetic conditions found that support or opposition to selective reproduction depended upon the participant's perceived quality of life and the quality of life they assigned to others with the same condition (Boardman & Hale, 2018). Individuals who supported selective reproduction often described experiences of social stigma, the impairments and intensive treatments associated with their condition, and limitations to relationships, employment, and housing as barriers to a full and successful life (Boardman & Hale, 2018). However, negative views of a condition did not necessarily mean individuals would support selective reproduction. Individuals who incorporated their condition into their identity tended to be ambivalent or opposed to selective reproduction as a societal problem of inaccurately using a single aspect of an individual to determine the value of the whole (Boardman & Hale, 2018).

CHAPTER 2

Reproductive-Aged Adults Diagnosed with Tuberous Sclerosis Complex (TSC): Understanding of Clinical Variability, Perceived Disease Burden, and Reproductive Decision-Making

Introduction

Preconception and prenatal counseling are important aspects of genetic counseling. As modern advances in genetics and reproductive technologies make it possible to not only diagnose genetic conditions before a child is born, but also to select embryos based on the presence or absence of a condition, it becomes even more important for genetic counselors to understand the thoughts and needs of clients making these reproductive decisions. While reproductive decisions always carry a level of uncertainty, individuals with highly variable genetic conditions must first contend with the chance of passing on the condition, and then with the uncertain genotype-phenotype relationship. Studies on reproductive decision-making have shown that the actual calculated genetic risk interacts with the perceived burden of the condition to determine an individual's reproductive choices (Hallowell & Richards, 1997). As a result, reproductive decisions would likely be highly influenced by an individual's knowledge of the clinical spectrum of a condition as well as their own experience.

Tuberous Sclerosis Complex

Tuberous Sclerosis Complex (TSC) is a highly variable multisystem disorder characterized by the growth of hamartomas (benign tumors) in the skin, brain, heart, lungs, kidneys, and eyes (Islam & Roach, 2015). Current estimates suggest that TSC affects between 1 in 6,000 to 1 in 10,000 births across all ethnicities (Northrup & Krueger, 2013). TSC is caused by an autosomal dominant mutation in one of two genes: *TSC1* which encodes the protein hamartin, and *TSC2* which encodes the protein tuberin (Nellist et al., 1993; vanSlegtenhorst et al., 1997). Hamartin and tuberin form a protein complex which

regulates cell growth, size, and proliferation through the mammalian target of rapamycin (mTOR) pathway (Caban et al., 2017). Mutations in either gene can result in the protein complex failing to inhibit mTOR activity resulting in hyperactivation and uncontrolled cell growth and proliferation (Caban et al., 2017).

While TSC is considered fully penetrant, the phenotype depends on the age of the individual, the number and size of lesions, the organs involved, and the exact location of the lesions (Whittemore et al., 1999). The skin and brain are the most commonly affected organs with lesions occurring in more than 90% of individuals (Wataya-Kaneda et al., 2017). Skin abnormalities range from mild skin differences such as hypomelanotic macules to disfiguring facial angiofibromas and fibrous plaques (Northrup & Krueger, 2013). Brain structure abnormalities include cortical tubers, white matter radial migration lines, subependymal nodules (SEN), and subependymal giant cell astrocytomas (SEGA) (Northrup & Krueger, 2013). Individuals with TSC may also have benign tumors in the heart (i.e., rhabdomyomas), kidney (i.e., angiomyolipomas [AMLs]), and eyes (i.e., retinal hamartomas) (Northrup & Krueger, 2013).

While the tumors associated with TSC are typically benign, they nonetheless have significant impact on morbidity and mortality (Amin, Lux, Calder, et al., 2017). One major health concern is kidney damage and possible renal failure resulting from angiomyolipomas, cysts, or in rare cases renal cell carcinomas, particularly in individuals over the age of 30 (Rentz et al., 2018). Around 30% of female TSC patients develop lymphangioleiomyomatosis (LAM), a lung disorder characterized by overgrowth of smooth muscle and replacement of the parenchyma with cysts resulting in progressive

loss of respiratory function, possible pneumothorax, and eventual respiratory failure (Frost & Hulbert, 2015; Moir, 2016). Seizures affect approximately 72 to 85% of individuals and persist regardless of treatment in roughly 60% of cases (Chu-Shore et al., 2010; Curatolo et al., 2015).

In addition to the physical manifestations of the condition, TSC-associated neuropsychiatric disorders (TAND) including developmental delay, intellectual disability, autism spectrum disorder, and behavioral disturbances can have a major impact on individuals and families (Curatolo et al., 2015). Approximately half of children diagnosed with TSC have autism spectrum disorder and/or intellectual disability ranging from borderline to profound (de Vries et al., 2018; Winterkorn et al., 2007). Among children with typical intellectual ability, 30 to 60% will experience learning difficulty (Curatolo et al., 2015; de Vries et al., 2018). Behavioral disturbances are common and include overactivity (45%), sleep difficulties (43.9%), impulsivity (42.7%), anxiety (33.3%), mood swings (29.8%) and depressed mood (19.2%) (de Vries et al., 2018). The rates and types of TAND also vary by age with a larger proportion of adults experiencing anxiety (50.9%), depressed mood (43.9%), and mood swings (40.8%) (de Vries et al., 2018). TAND are some of the most difficult symptoms for families to manage and parents often report significant stress due to their child's intellectual deficits and behavioral problems (Kopp et al., 2008).

While these physical and psychological symptoms would clearly impact an individual's daily life, perceptions of quality of life have only recently been assessed. Jansen et al. (2017) presented the results of a survey assessing quality of life in 111

patients including 45 adults with TSC. They found that 55.6% of adults with TSC reported that their career, education, and interpersonal relationships outside the family had been adversely affected by TSC. Nearly half (48.6%) reported anxiety or depression, and 40% reported significant pain or discomfort. These preliminary findings suggest that TSC has a substantial impact on individuals' health and wellbeing. While there are currently no studies assessing the impact of quality of life on reproductive decisions in TSC patients, the findings of Jansen et al. suggest that perceived disease burden may be an important factor in family planning.

Reproductive Decision Making

As an autosomal dominant condition with nearly full penetrance, individuals with TSC have a 50% chance of passing on their condition to each of their children. However, while the genotypic risk is clear, the phenotypic risk is less certain. In some individuals, the condition is so mild that it is only diagnosed when a more severely affected family member is born (Caylor et al., 2018; Fox et al., 2017; Robyr et al., 2006). This high level of phenotypic variability poses a challenge when adults with TSC are faced with family planning decisions. Due to the rarity of the condition and high *de novo* mutation rate of roughly 70%, adults with TSC may have no exposure to the phenotypic range of the condition outside their own subjective experience. Individuals who perceive their condition as having a significant negative impact on their lives may view the possibility of passing on TSC to a child more negatively than individuals who have had a more neutral or positive experience.

While reproductive decisions of individuals with TSC have yet to have been studied, research into other dominant conditions with variable expressivity can provide insights into how individuals with TSC may approach reproductive decisions. One study found that 62% of individuals diagnosed with Marfan syndrome (a connective tissue disorder affecting the bones, skin, eyes, and cardiovascular system) felt the condition significantly influenced reproductive decision-making (Peters et al., 2002). This was particularly true for individuals with a family history or those who were diagnosed before the age of fifteen. The influence of Marfan syndrome on reproductive decision-making correlated with the perception that Marfan syndrome had significant negative consequences on the affected individual's life (Peters et al., 2002). Additionally, individuals with a family history and therefore presumably more exposure to possible negative consequences of the condition were less likely to have children than those without a family history (Peters et al., 2002).

A study on individuals affected by Neurofibromatosis 1 (NF1) had similar findings with participants stating that the variability of the condition was a major complicating factor in family planning (Benjamin et al., 1993). Like TSC, NF1 is characterized by patches of pigment variation and the growth of benign skin tumors which can range from mild cosmetic differences to severe disfigurement. Affected individuals may also experience learning difficulties (30% of cases) and epilepsy (4% of cases). Benjamin et al. (1993) found that a majority of their study respondents perceived themselves as more severely affected than medical classification would suggest, particularly those who were concerned about the cosmetic aspects of the condition. NF1 posed a significant burden

for many respondents with 63% reporting difficulty in school, 48% reporting anxiety during adolescence due to cosmetic symptoms, and 17% reporting teasing. In a similar study, severely affected individuals reported that they did not see themselves as likely to get married due to their condition, indicating that NF1 had a negative influence on their quality of life (Ponder et al., 1998). When asked about hypothetical children, half of severely affected individuals reported that they would not want to have children with NF1 (Ponder et al., 1998). The study also found that affected parents who had more severely affected children reported feelings of distress and guilt for having known the risk of passing on NF1 without fully understanding the chance of increased severity in their child (Ponder et al., 1998).

Study Aims

To better counsel adult clients with TSC, genetic counselors need to understand what factors weigh most heavily in their family planning decisions. Adults with TSC would have to consider their knowledge of TSC, their personal experience with the condition, and their desired family structure when making family planning decisions. It is not currently clear whether individuals with a family history of TSC perceive the chance of passing on TSC to a child differently from individuals who have a *de novo* mutation. Additionally, it is unclear whether adults with TSC are familiar with reproductive options such as preimplantation genetic diagnosis (PGD) or prenatal genetic diagnosis. To utilize these options, an individual with TSC would need to know their genetic mutation. It is not currently known what percent of adults with TSC know their genetic mutation status. This study addresses these gaps in understanding through an exploratory mixed-methods

survey utilizing an anonymous online questionnaire to assess study participants': 1) familiarity with the symptoms of TSC, 2) understanding of the risk of passing on TSC to a child, 3) perceived disease burden/quality of life, and 4) family planning considerations.

Methods

Participants

The overarching goal of this research is to better understand how adults diagnosed with TSC make reproductive decisions. Therefore, participation was limited to individuals who have been diagnosed with TSC who are between the ages of 18 to 45 years. While we recognize that an age cut-off of 45 may not encompass all adults with TSC who may be making family planning decisions, we wanted to limit the age range to those who were most likely to be making current or future decisions.

Recruitment for the survey was conducted with the aid of the TS Alliance, a non-profit dedicated to advocating for TSC, supporting research, and providing information and support for affected individuals and families. The survey was advertised through flyers (Appendix A) distributed at the TS Alliance table at the 2018 World TSC Conference in Dallas, TX on July 26 - 29, 2018. Digital copies of the flyer were also distributed through the TS Alliance Facebook groups, online community support pages, and through the monthly "Adults with TSC" email newsletter. Recruitment advertisements were posted from July to November 2018. To increase survey participation, a $25 Amazon e-gift card drawing was offered as incentive. Participants who chose to enter the drawing provided either an email or phone number where the e-gift card could be delivered. At the end of

the survey period, all entries were run through an online random selection tool and the e-gift card was sent to the winning phone number or email. Direct financial or academic compensation for completing the survey was not offered to avoid coercion.

Participation in the survey and drawing was completely voluntary. Consent was obtained through the questionnaire welcome page (Appendix B) which outlined the goals and format of the survey. Participants were informed that they could stop at any time or skip any question except for the participation eligibility questions. The welcome page stated that by clicking "next" to proceed to the questionnaire, the participant was providing informed consent. To establish participation eligibility, the questionnaire begins with two screener questions. Individuals who did not meet participation eligibility were automatically redirected to a thank-you page and did not proceed with the questionnaire.

A total of 224 individuals attempted to participate in the online survey. The first eligibility question screened out seven individuals who did not have a diagnosis of TSC, leaving 217 individuals to move on to the next screener question. The second eligibility question screened out another seven individuals who were not aged between 18 and 45, leaving 210 to complete the questionnaire. Four people did not complete any of the questions after the first two questions and were manually deleted from the data set. Of the 206 individuals who answered Question 3, two individuals answered that their current age was over 45 thereby disqualifying themselves from participating in the survey. These individuals' responses were manually deleted from the data set leaving 204 participants eligible for the study. Twenty-nine participants did not provide any symptoms of TSC they

experience. Due to the important role participants' symptoms play in our research questions, we manually removed these 29 responses from the data set leaving 175 participants in the final analysis. Participant demographics are summarized in Table 2.1.

Instrumentation

In order to assess study aims, we conducted an anonymous online mixed-methods survey. The purpose-designed questionnaire was hosted on a password-protected SurveyMonkey.com account. The questionnaire included twenty-four questions which covered demographics, knowledge of TSC, symptoms of the individual and affected family members, reproductive decisions and quality of life (Appendix B). Personally identifiable information was not collected in this survey. The SurveyMonkey software has skip logic which allowed us to use the participants' responses to certain questions to determine if they should proceed to the next question or be redirected to a later part of the questionnaire if the next question did not pertain to them. Therefore, while the questionnaire included 24 total questions, not every participant was asked each question. Our questionnaire included a purpose-designed disease burden/quality of life instrument. The questions included in the disease burden/quality of life instrument were based on factors that were included in the quality of life survey by Jansen et al. (2017).

Procedures

To assess knowledge of TSC, participants were asked if a listed symptom was or was not a symptom of TSC. Correct answers were given a score of "1" while incorrect or blank answers were given a score of "0" for a total of 24 possible points. To assess familiarity with symptoms of TSC, participants were asked if they or an affected family

member experienced the specified symptom. Symptom severity scores were calculated for participants and family members by adding the total number of TSC symptoms experienced to create an overall score. Participants were also given a score for facial symptom severity (i.e., presence of angiofibromas and forehead plaques). Some participants who did not previously state that they had a family member with TSC nonetheless selected certain TSC associated symptoms were present in family members. Since some symptoms (i.e., seizures) could be present in family members who did not have TSC, we filtered responses so that only the responses from individuals who stated they had an affected family member were counted and scored. Open-ended questions eliciting a numerical response (i.e., Questions 3, 7, 8, 11, and 13) were standardized by converting text to a number (e.g., "one" was converted to "1"), rounding to whole numbers (e.g., "7½" was converted to 8), and selecting the higher number of a range (e.g., "4 to 6" was converted to 6). Disease burden was assessed by asking participants to rate how often they agreed with a statement on a scale of "never" to "very often." Responses were converted to a five-point Likert score. Negative statements were scored one for "never" to five for "very often." Positive statements were scored in reverse with a score of five for "never" and one for "very often." Responses were added together to create a disease burden score with lower values representing less burden and higher values representing more burden. While most questions were quantitative in nature, questions regarding reproductive decisions combined quantitative measurements with qualitative, open-ended responses. We chose to use mixed-methods to better identify themes that influenced participants' reproductive decisions. Mixed-methods research combines

quantitative and qualitative methodology to investigate questions that cannot be sufficiently answered by a single method alone (Castro, Kellison, Boyd, & Kopak, 2010).

Data Analysis

Data was analyzed using SPSS Statistics software (Armonk, NY: IBM Corporation). Descriptive statistics were used to describe data, inferential statistics were used to look at group differences, and grounded theory was used to analyze open-ended questions. Open-ended responses were read by the principal investigator and thematically analyzed and scored.

Results

Participant Demographics

Our survey population of 175 individuals was normally distributed between 18 to 45 years of age with a mean of 31.85 years (SD = 7.65) and a median of 32 years. Sex was skewed toward females (n = 137, 78.29%); only one-fifth of the population was male (n = 35, 20.00%) and a small minority (n = 3, 1.71%) preferred not to answer their sex. A majority of participants (62.79%) were either married (n = 70, 40.70%) or in a serious relationship or engaged (n = 38, 22.09%). Participants were highly educated with 42.44% having a bachelor's degree or higher. See Table 2.1 for more detailed participant demographics. Fifty-three participants (30.29%) currently have children. The average number of children was 1.79 with a median of two children. Fifty-eight participants (33.14%) reported at least one affected family member. Eleven (18.96%) of the participants were from multigenerational families with both a parent and at least one

child diagnosed with TSC. Participants' current family structure is summarized in Table 2.2.

Diagnosis of TSC

When asked at what age they were diagnosed with TSC, seven (4.00%) reported they were diagnosed prenatally, 43 (24.57%) reported they were diagnosed under the age of one, and 125 (71.43%) reported they were diagnosed over the age of one. Of those who were diagnosed over the age of one, answers ranged from one to 40 years of age with an average age of 14.66 (SD = 10.69) and a median age of 12. The median age at diagnosis for the whole survey population was seven. The average age at diagnosis was not calculated for the whole survey population due to the difficulty of calculating ages for prenatal diagnoses, and the fact we did not specifically ask the age in months for individuals diagnosed under the age of one. Figure 2.1 shows the range of ages at diagnosis.

When asked if they have had genetic testing for TSC, 102 (58.62%) responded yes, 55 (31.61%) responded no, and 17 (9.77%) were uncertain. Genetic testing results are summarized in Figure 2.2. A pathogenic variant was found for 63.73% of those who had testing, with the majority having a *TSC2* pathogenic variant (n = 39, 38.24%). A pathogenic variant in *TSC1* was identified in 26 participants (25.49%). Sixteen individuals (15.69%) reported that they had No Mutation Identified (NMI) by genetic testing while another four individuals (3.92%) had a Variant of Uncertain Significance (VUS).

Knowledge of TSC

When asked about the recurrence risk of TSC, most individuals (n = 147, 85.96%) knew that there was a 50% chance of passing on TSC to a child. Of the individuals who did not correctly answer this question, three (1.75%) believed it was a 0% chance, twelve (7.02%) believed it was a 25% chance, seven (4.09%) believed it was a 75% chance, and two (1.17%) believed it was a 100% chance. A total of 174 participants answered "yes" or "no" to at least one of the symptoms associated with TSC. The average knowledge score was 20.27 out of 24 possible points (86.64%). Scores ranged between 3 (12.50%) and 24 (100.00%) with a median of 22 (91.67%). Figure 2.3 shows the percent of participants who correctly identified each symptom of TSC. The three most highly recognized symptoms of TSC were cortical tubers (98.85%), AMLs (98.28%), and seizures (97.70%). The three least recognized symptoms were forehead plaques (77.01%), shagreen patches (77.01%), and LAM (75.29%).

Since LAM disproportionately affects one sex, we compared the responses of females to males for this symptom. A chi-square test for association was conducted between sex and correctly identifying LAM as a symptom of TSC. All expected cell frequencies were greater than five. There was a statistically significant association between sex and correctly identifying LAM as a symptom, $\chi 2(1) = 7.49$, $p = .006$. There was a negative association between sex and correctly identifying LAM as a symptom, $\phi = -.21$, $p = .006$, with females answering this question correctly more often than males.

Reported Symptoms

Symptoms experienced by participants are summarized in Table 2.3. The three most commonly reported symptoms included angiofibromas (n = 142, 81.14%), ash-leaf spots (n = 132, 67.31%), and AMLs (n = 123, 70.29%). Cortical tubers were reported by 102 participants (58.29%). Seizures, which are often associated with cortical tubers, were reported with similar frequency (n = 89, 50.86%). LAM was reported by 40 individuals (22.86%). Of those 40 individuals, two (5.0%) were male. Thirty-one participants (17.71%) reported other symptoms not included on the provided symptom list. Symptoms reported in the "other" category included dental pits, subependymal giant cell astrocytomas (SEGA), polycystic kidney disease, and mental health issues. Since not all participants were asked if they experience these symptoms of TSC, we did not calculate frequencies of these symptoms.

A total of 52 individuals provided symptoms experienced by family members with TSC (Table 2.3). The three most common symptoms reported in family members included seizures (n = 36, 69.23%), ash-leaf spots (n = 35, 67.31%), and cortical tubers (n = 31, 59.62%). Intellectual disability and autism were reported more frequently in family members than participants (44.23% vs. 16.57%, and 30.77% vs. 10.86% respectively). Skin findings (i.e., angiofibromas, forehead plaques, and shagreen patches) were reported more frequently in participants than family members.

Perceived Disease Burden

Over half of participants (58.58%) perceived their symptom severity as mild or very mild (Figure 2.4). A minority of participants (10.06%) perceived their symptoms as

strong or severe. In addition to the participant's perceived disease burden, we employed a purpose-designed instrument to measure disease burden/quality of life in individuals diagnosed with TSC. This instrument consisted of 14 questions. The scale had a high level of internal consistency, as determined by a Cronbach's alpha of .873. A Pearson's product-moment correlation was run to assess the relationship between symptom severity and disease burden/quality of life as measured by the instrument. Preliminary analyses showed the relationship to be linear with both variables normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$), and there were no outliers. There was a statistically significant, small positive correlation between symptom severity and disease burden/quality of life, $r(168) = .256$, $p = .001$, with symptoms severity explaining 6.55% of the variation in disease burden/quality of life.

The highest possible score on the disease burden/quality of life instrument was 70 and the lowest possible score was 14. Scores ranged between 16 and 66. Participants had an average score of 39.83 (SD = 11.33) and a median score of 40. Results of the disease burden/quality of life instrument are summarized in Figure 2.5 and Table 2.4.

Reproductive Decisions

Desired number of children.

When asked whether they would like to have a child or more children in the future, 78 (45.09%) responded yes, 70 (40.46%) responded no, and 25 (14.45%) were undecided. The 96 participants who answered "yes" or "undecided" were then asked how many total children they were considering having. Nineteen (19.79%) responded one, 51 (53.13%) responded two, 16 (16.67%) responded three, 8 (8.33%) responded four, and 2 (2.08%)

responded five or more. The average number of desired children was 2.25 and the median number was two. When asked if their desired number of children would be different if they did not have TSC, 71 (40.57%) responded yes, 65 (37.14%) responded no, and 39 (22.29%) were uncertain. When asked how many total children they would have if they did not have TSC, 6 (5.94%) responded one, 35 (34.65%) responded two, 33 (32.67%) responded three, 13 (12.87%) responded four, and 14 (13.86%) responded five or more. The average number of desired children if the participant did not have TSC was 3.12 and the median number was three.

To assess what factors might be contributing to the participants' current desired number of children, we performed several regression models (Table 2.5). None of the factors investigated had a statistically significant effect on the desired number of children. We also wanted to assess whether the participants' disease burden/quality of life score had an effect on how many children they desired if they did not have TSC. A linear regression established that disease burden/quality of life score did not statistically significantly predict total number of children desired if the participant did not have TSC, $F(1, 97) = .362$, $p = .549$. Disease burden/quality of life score accounted for 4.0% of the explained variability in total number of children desired if the participant did not have TSC.

Reproductive methods being considered.

Participants who stated that they were undecided or planned to have future children were asked to select which reproductive methods they were considering out of traditional conception, adoption, using donor gametes or embryos, and preimplantation

genetic diagnosis (PGD). Participants were able to select more than one option. A total of 102 participants provided a response (Figure 2.6). Traditional conception was selected by 54 (52.94%), adoption was selected by 46 (45.10%), using donor gametes or embryos was selected by 18 (17.65%), and PGD was selected by 51 (50.00%). Two individuals (1.96%) selected all four options. Of the participants who selected only one option, 19 (18.63%) were only considering traditional conception, 11 (10.78%) were only considering adoption, 6 (5.88%) were only considering using donor gametes or embryos, and 17 (16.67%) were only considering PGD. To assess what factors might be contributing to the participants' choice of reproductive method, we performed several regression models (Table 2.6). None of the factors investigated had a statistically significant effect on the choice of reproductive method.

Participants' stated factors deciding reproductive method.

Eighty-nine individuals provided an open-ended response for what factors influenced which reproductive method they were considering. Thematic analysis revealed eight themes (Table 2.7). The most common theme was a desire to not pass on TSC to a child which was expressed by 37.08% of respondents. Personal health or medical advice was another major factor expressed by 25.84% of individuals. Participants who were classified into this theme mentioned concerns about kidney health (i.e., increased strain on diseased kidney), lung health (i.e., increasing the chance of developing LAM), or controlling seizures during pregnancy. Fertility issues, which affect 10.11% of the respondents, were categorized into a separate theme from personal health due to the fact these individuals have fewer reproductive options. Fertility issues included advanced

maternal age and personal history of hysterectomy due to complications of TSC. For individuals who received a NMI result, PGD is not technologically possible. Six individuals recognized this limitation. Other themes included desire for biological children, financial concerns, thoughts or desires of partner, and ethical concerns. Responses which could not be categorized into one of the eight themes were classified as "other."

Interest in prenatal testing.

Participants showed a high level of interest in prenatal testing of a hypothetical future pregnancy (Figure 2.7). A one-way ANOVA was conducted to determine if those who would choose to have, would not choose to have, and who were uncertain about having prenatal testing had different symptom severity scores. Participants were classified into three groups: those who would choose to have prenatal testing (n = 115), those who were uncertain about having prenatal testing (n = 26), and those who would not choose to have prenatal testing (n = 29). Symptom severity score increased from those who would not have prenatal testing (M = 5.59, SD = 3.19), to those who would have prenatal testing (M = 6.60, SD = 2.97), to those who were uncertain about having prenatal testing (M = 6.85, SD = 2.96), in that order, but the differences between these groups were not statistically significant, $F(2, 167) = 1.565$, $p = .212$.

Participants' stated factors for prenatal testing decision.

A total of 142 individuals provided an open-ended response for what factors influenced their decision. Thematic analysis revealed eight themes (Table 2.8). The most common theme was a desire to be informed or prepared which was expressed by 47.18% of respondents. Respondents who were classified into this theme frequently mentioned

their own difficult diagnostic odyssey and the benefit of their child growing up with a known diagnosis. Another major theme identified in 21.13% of responses was to possibly consider termination. While only three individuals directly stated that they would terminate the pregnancy, others stated that they would not want to be responsible for passing on TSC to a child or that they would not want a future child to have to face the same decision as themselves. Other individuals stated that they were accepting of whatever happens (8.45% of responses). Other themes included ethical concerns, the risk of invasive testing, financial concerns, testing not being technologically possible in their case, and previous experience with prenatal testing.

Discussion

In this study we set out to assess study participants': 1) familiarity with the symptoms of TSC, 2) understanding of the risk of passing on TSC to a child, 3) perceived disease burden/quality of life, and 4) family planning considerations. To our knowledge, this is the only study to assess the familiarity of individuals diagnosed with TSC with the broad spectrum of symptoms associated with the condition. A majority of our study population was able to recognize all of the symptoms we assessed. Unsurprisingly, 98.85% of participants were familiar with cortical tubers, the hallmark symptom from which the condition derives its name. Interestingly, the second most recognized symptom was AMLs, which was identified by more participants (98.28%) than seizures (97.70%), ash-leaf spots (95.40%), and angiofibromas (94.25%). This result is somewhat surprising since AMLs are estimated to affect fewer individuals with TSC (52%), than

seizures (85%), ash-leaf spots (>90%), or angiofibromas (75%) (Kingswood et al., 2019; Wataya-Kaneda et al., 2017). This disconnect between the prevalence of AMLs in the population and the familiarity with the condition is possibly due to the high morbidity and mortality associated with the condition.

A recent study investigating TSC patients' and parents' knowledge about AMLs had similar results to our study with 93% of individuals reporting that they were aware of AML as a symptom of TSC (Cockerell et al., 2018). However, Cockerell et al. (2018) also found that while a majority of patients recognized AML as a symptom of TSC, 42% did not know about the associated hemorrhage risk, and 30% were not receiving the appropriate renal imaging. Therefore, it is possible that healthcare providers are diligently informing individuals with TSC about the risk of developing an AML due to the high morbidity and mortality, but patients may not be fully appreciating the potentially life-threatening nature of the condition. While it has long been known that the risk of hemorrhage increases with larger lesion size (typically lesions over 4 cm), the increased risk associated with pregnancy has recently been gaining more attention (Ahn, Roberts, Navaratnam, Chung, & Wood, 2019; Wang, Li, Peng, Gou, & Fan, 2018). This risk should be emphasized to women with TSC so they can receive appropriate care and monitoring during pregnancy. Our study did not directly assess whether participants were aware of the possible severe complications associated with AMLs; however, in our open-ended responses to the factors that influenced choice of reproductive method, several individuals mentioned concerns about AMLs (see Table 2.7, Personal Health or Medical Advice example response). Our study design does not allow us to assess whether these

individuals represent the understanding of the whole study population, or a smaller subset like what was found in Cockerell et al.

Another notable finding from our knowledge assessment was the relatively low level of familiarity of study participants with LAM. Only 75.29% of the participants correctly identified LAM as a symptom of TSC. LAM affects around one third of women with TSC, with symptom onset during the reproductive years when women are making family planning decisions (Gupta & Henske, 2018; Moir, 2016). Since LAM disproportionately affects women, we compared the responses of males and females to this question. We found a statistically significant difference with women being more likely than men to recognize LAM as a symptom of TSC. This result suggests that medical professionals including genetic counselors need to emphasize the risk of developing LAM, especially to men with TSC. While women are far more likely to develop LAM, in rare cases men may also develop the condition (Adriaensen, Schaefer-Prokop, Duyndam, Zonnenberg, & Prokop, 2011). In our study, two of our male participants reported having LAM. Even if men are unlikely to develop LAM, there is still risk to future daughters that should be understood before reproductive decisions are made.

The 50% recurrence risk of TSC was understood by a majority of our study participants (85.96%). Three individuals (1.75%) believed that there was no chance of having a child with TSC. While it is possible that an individual can have TSC due to a somatic mutation and therefore not necessarily be at risk of passing TSC on, this was not the case for these individuals. One individual had a *TSC1* mutation, one did not know his or her genetic testing result, and the last individual had not had genetic testing. These

individuals' belief that they could not have a child with TSC suggests they either do not understand the genetic nature of their condition, or they are unrealistically optimistic about their personal chance of having an affected child. Twelve individuals (7.02%) believed that the recurrence risk was 25%. It is not clear if these individuals mistakenly believed the condition to be recessive, or if they were answering based on a perceived personal risk. Finally, seven individuals (4.09%) believed the recurrence risk was 75%, and two individuals (1.17%) believed the recurrence risk to be 100%. These individuals' responses were likely based on the perception that their personal chance of having a child with TSC was high. Our study did not directly ask participants for their reasoning for the recurrence risk. Therefore, future studies should directly ask participants about why they believed the recurrence risk was the number they selected to assess whether individuals have a clear understanding of the genetics of TSC, or are answering from a more emotional standpoint.

Over half of our study participants perceived their symptom severity as mild or very mild. This result was consistent with the frequencies of symptoms reported. While literature on TSC suggests over 90% of individuals have cortical tubers and 85% of individuals have seizures (Wataya-Kaneda et al., 2017), in our study population only 58.29% reported cortical tubers and 50.86% reported seizures. Likewise, the more severe neurological complications of intellectual disability and autism were uncommon in our study population (16.57% and 10.86% respectively), but closer to the published frequency of around 50% in affected family members (44.23% and 30.77% respectively). The most common symptoms in study participants were angiofibromas (81.14%), ash-leaf spots

(75.43%), and angiomyolipomas (70.29%). Unlike seizures or intellectual disability, mild skin lesions or AMLs may go unnoticed by both the individual and their health provider unless a complication occurs. While we did not directly ask study participants how they came to their diagnosis of TSC, in open-ended responses several individuals mentioned a long diagnostic odyssey or discovering their condition after having a child with TSC. Such statements are consistent with having a milder phenotype. These results are unsurprising given the methods and format of our study. It is unlikely that individuals with severe intellectual disability would be actively participating in the online support groups from which we recruited study participants.

Our purpose-designed disease burden/quality of life instrument provided valuable insights into the experience of adults with TSC. A majority of participants reported that they felt different from those around them, that they were frustrated by their symptoms, that their symptoms made them anxious, and that they thought about their TSC at least some of the time. In addition to the psychological impact on quality of life, TSC also impacted the physical quality of life for many participants. Sleep disturbance was common with nearly 40% reporting that they often or very often have difficulty sleeping. Around half of participants reported experiencing pain because of their TSC at least some of the time. However, while participants were clearly impacted by their diagnosis, they also had a mostly positive outlook. A majority of participants felt like they were in control of their lives, felt good about their social life, and felt comfortable meeting new people. The majority of participants also felt like they had the support they needed, which is unsurprising given the fact we recruited our participants from support groups.

Around 60% of our study population was considering having future children with the average desired number of children equaling 2.25. When asked if this number would be different if the individual did not have TSC, around 60% said yes or that they were uncertain. If hypothetically the individual did not have TSC, the average number of desired children was 3.12. To assess what factors may be influencing these differences in desired number of children, we performed several regression models looking at the effect of symptom knowledge score, symptom severity in the participant and family members, and disease burden/quality of life scores. None of the factors we analyzed had a statistically significant effect on the desired number of children. This suggests that, at least for our study population, the desire for children was independent from the participant's experiences with TSC that we measured.

When asked what reproductive methods they were considering, most participants stated they were considering more than one reproductive option, suggesting a strong desire to have children in general. Seventeen individuals (16.67%) were only interested in having a child through PGD. This relatively high level of interest in PGD suggests a strong desire to have a biological child who is not affected by TSC. Our survey did not assess whether participants were familiar with PGD before participating in the survey and therefore would be aware of the logistics, limitations, and cost associated with the procedure. The desire for a biological child was also clearly evident from the number of participants who stated they were only considering traditional conception (19/102, 18.63%). It is not clear whether individuals who stated they were only considering traditional conception are 1) not concerned about having a child with TSC, 2) are

concerned, but are willing to risk the odds, or 3) are concerned, but considering having prenatal testing and terminating an affected pregnancy. Adoption was the only method considered for 10.78% of the population. Individuals considering adoption likely have a strong desire for a child, but may not be able to carry a pregnancy, or may have less of a psychological need to have a biological relationship to the child either through inheritance or through carrying the pregnancy. Finally, six participants (5.88%) were only considering using donor gametes or embryos. In one open-ended response, the participant mentioned that they were in a same-sex relationship. When designing our questionnaire, we failed to account for same-sex couples. We therefore cannot determine if the individuals who stated that they were only considering using donor gametes or embryos are same-sex couples or are heterosexual couples interested in having the experience of a pregnancy without the risk of passing on TSC to a child.

In order to assess what factors may be influencing these choices of reproductive methods, we performed several regression models. There was no significant effect of symptom severity in the participant, symptom severity in family members, or disease burden/quality of life scores on the choice of reproductive method (Table 2.6). Thematic analysis of participants' responses to what factors influenced their choice of reproductive method revealed eight themes (Table 2.7). The most common theme mentioned by 37.08% of participants was a "desire to not pass on TSC to a child." While these individuals could be considering adoption or use of donor gametes or embryos, PGD was often specifically mentioned in their open-ended responses.

A recent review of patient decision-making factors regarding PGD found that patients were highly motivated by the prospect of a healthy child free from the genetic condition; however, patients recognized the decision to use PGD was complex (Genoff Garzon, Rubin, Lobel, Stelling, & Pastore, 2017). PGD requires commitment of time, money, and emotional resources which may or may not result in a baby. Ethical concerns were also a complicating factor. Some people expressed ethical concerns about discarding affected embryos. Others stated they felt ethically obligated to use available technology to ensure their child would not be affected by a genetic condition. Our study participants provided similar themes to those identified by Genoff Garzon et al. including financial and ethical concerns about PGD. Technology was also a concern, however in our study population the concern was that PGD was unavailable for them personally. PGD cannot be used unless the individual has an identified pathogenic mutation. Therefore, our participants who had NMI or a VUS would be unable to utilize this technology.

The second major theme for their choice of reproductive method mentioned by a 25.84% of participants was “personal health or medical advice”. Most responses in this category mentioned that pregnancy would be dangerous for them due to AMLs or LAM, or that medical professionals recommended they should not have children. As mentioned previously, our study population seemed highly informed about symptoms of TSC and the associated risks. As demonstrated in the example response for this theme, several women recognized that the risk of AML rupture increased with pregnancy. The chance of exacerbating LAM also increases with pregnancy. Therefore, these individuals were often considering adopting children.

The third major theme was the "desire for biological children" (19.10% of responses). The majority of participants (around 85%) wanted to have a biological child. Around a third of participants were only interested in having a biological child, either through traditional conception or through PGD. As mentioned in the example response for this theme, individuals who desired biological children often stated that they always wanted to be a parent. Since around 30% of our participants were diagnosed during their reproductive years, the desire for biological children likely predates their diagnosis of TSC. In our study we did not directly ask whether individuals have changed their mind about family plans over the course of their life as they learned more about TSC.

One theme that was revealed through thematic analysis that we had not previously considered was the impact TSC may have on fertility. As described in the example response for the theme of "fertility issues," some individuals had complications of TSC which limited the reproductive options available. Rare uterine tumors such as perivascular epithelioid cell tumors (PEComas) or uterine LAM can occur in women with TSC (DeLair & Soslow, 2016). While the incidence of these tumors is not clearly defined in the literature, recent studies suggest they are not uncommon, especially in women with LAM. A study comparing 20 LAM patients found that 90% of the women who had been diagnosed with pulmonary LAM have uterine LAM as well (Hayashi et al., 2011). Another study found that 18.1% of women under the age of 40 with TSC-associated LAM had uterine tumors (Taveira-DaSilva, Rabel, Gochuico, Avila, & Moss, 2011). In an epidemiological study of Japanese patients with TSC, examination of the uterus of 51 women over the age of 20 by CT and MRI found that 57% had uterine tumors; three

women had already undergone radical hysterectomies because of multiple leiomyomas, PEComas, and carcinomas (Wataya-Kaneda, Tanaka, Hamasaki, & Katayama, 2013). While there are no consensus guidelines on how to treat uterine PEComas or LAM, hysterectomy is often performed (Kudela, Biringer, Kasajova, Nachajova, & Adamkov, 2016; Shan et al., 2019; Taveira-DaSilva et al., 2011). Therefore, for women with TSC the ability to carry a pregnancy may be at risk due to complications of the condition. Additionally, several women mentioned delaying starting a family due to health concerns (i.e., seizure control) and therefore having limited fertility due to age. These results suggest fertility concerns and gynecological health should be addressed when counseling women with TSC, especially during their reproductive years.

Our study population showed a high level of interest in prenatal testing with 67.44% stating they would have prenatal testing in a hypothetical future pregnancy and 15.12% stating they were uncertain. When we compared symptom severity scores to interest in prenatal testing, we found a positive trend with severity scores increasing from those who are not interested in testing to those who are interested in testing. However, the differences in severity scores were not statistically significant. Thematic analysis of factors that participants stated influenced their decisions about prenatal testing revealed eight themes.

The most common theme which was expressed in 47.18% of responses was “being informed or prepared.” Many of the responses which were classified into this theme mentioned the long diagnostic odyssey that the participant experienced to reach their TSC diagnosis. These participants stated that they did not want their child to go through

the same experience. Like the example response for this category, many participants stated that they wanted to know before the baby was born to obtain the appropriate medical care for their child from birth and to prepare their lives for the possibility of a more severely affected child.

The second most common theme which was expressed by 21.13% of participants was considering termination if the pregnancy was affected. Only three participants directly stated that they would terminate an affected pregnancy. Other participants who were placed into this theme stated that they did not want to be responsible for passing on TSC to a child. Due to the context of the question, these responses were assumed to mean that the participant would terminate the pregnancy to prevent their child from being born with TSC. One participant stated that they would not want their child to have to face the same decision. This participant was therefore preventing their child from having the possible psychological burden of deciding whether or not to risk having a more severely affected child by ensuring that their child was born without TSC.

The third most common theme was being accepting of whatever happens which was expressed by 8.45% of the participants. This theme was the most common response of individuals who would not consider prenatal testing. Many individuals stated that they would be happy to be a parent no matter what the outcome. Others stated that the outcome was in God's hands.

In addition to the three major themes, we identified five minor themes. Four of the themes were reasons why individuals were not interested in prenatal testing. These themes included ethical concerns about testing, concerns about the risk of invasive

testing, financial concerns, and testing not being technologically possible in their case. The final theme identified was previous experience with prenatal testing which was expressed by individuals who were interested in prenatal testing. All four of these individuals had previously used prenatal testing for TSC in a pregnancy. At least one of these participants decided to terminate the affected pregnancy (see example response, Table 2.8).

Practice Implications

The results of this study suggest there are several areas where genetic counselors and other healthcare providers can help fill in knowledge gaps for adults with TSC. In particular, our study showed that men with TSC are less familiar with lymphangioleiomyomatosis. While men are much less likely to develop LAM, it is still a potential health risk. LAM would also pose a risk to future daughters, and therefore men should be aware of this risk before making family planning decisions. It is also important to emphasize the 50% recurrance risk to individuals with TSC so they can make informed reproductive decisions. While most of our study participants were aware of this risk, around 15% believed the risk to be higher or lower than 50%. These individuals might be making reproductive decisions that they otherwise would not make if they knew the actual recurrence risk. Finally, our thematic analysis revealed that fertility issues for individuals with TSC should be addressed more often by healthcare providers. In particular, women of reproductive age should be informed about the chance of developing uterine tumors which may require surgical excision or hysterectomy. If

women are made aware of this potential complication of TSC, they might decide to start their family at a younger age.

Our study showed that individuals with TSC are highly motivated to have biological children. Many of our study participants were interested in using available reproductive technologies such as PGD or prenatal diagnosis. While many people view these technologies in a very positive light, they still have limitations and barriers to their use. One major barrier is cost, particularly for the IVF which is required to perform PGD. Another important barrier is the fact that individuals must know their pathogenic variant to utilize these technologies. In our study, over half of the participants (58.29%) had genetic testing. However, this number is less than the number of individuals who stated that they wanted prenatal testing in a future pregnancy (67.44%). It is important to emphasize to individuals with TSC that a pathogenic mutation must first be identified in the affected parent before PGD or prenatal testing can be performed. While the parent could decide to have genetic testing at the time of pregnancy, this could add delay to the prenatal testing process which could potentially eliminate the possibility of terminating a pregnancy if the family wished.

Genetic counselors also need to emphasize that genetic testing may not find a pathogenic variant. In our study population, a pathogenic variant was identified in only 63.73% of individuals tested. This number is also below the number of individuals who were interested in prenatal diagnosis, indicating that some of the individuals who would want prenatal testing would not be able to utilize this technology. While it is possible to identify affected pregnancies by ultrasound or fetal MRI (Dragoumi, O'Callaghan, &

Zafeiriou, 2018), it is important to emphasize to parents that there are limitations to all technologies and prenatal diagnosis may not be possible in all cases. It is possible that some individuals do not realize this limitation and are making reproductive decisions based on the assumption that these technologies would be available.

Study Limitations

Our study had several limitations. One limitation is the fact that participants were recruited through the World TSC Conference and support groups and therefore are more likely to be highly engaged in their diagnosis. This high level of engagement likely lead to participants being more aware of the range of clinical symptoms that can occur in TSC and more likely to know other individuals with TSC symptoms different from their own. This high level of awareness is likely not the case in the general population of individuals with TSC. Therefore, our results may not be representative of the adult TSC population as a whole. The high level of awareness of symptoms of TSC might also be inaccurate due to the fact this survey was conducted online. It is possible that participants researched symptoms of TSC as they were taking the survey, thereby skewing the results of the TSC symptoms knowledge score.

Participant demographics were also somewhat skewed. A large majority (78.29%) of study participants were female. This result is unsurprising given the fact that women tend to be more active in support groups than men. However, since men and women are equally affected by TSC, our results may not be reflective of the adult TSC population as a whole. Our participants were also highly educated with 42.44% having a bachelor's degree or higher. This is significantly higher than the 34% of Americans who have a

bachelor's degree or higher according to the US Census Bureau (Schmidt, 2018). This education bias is likely also due to the fact we recruited from support groups and the World TSC Conference which are more likely to attract highly engaged and educated individuals. Due to the high level of education in our study group, it is possible that the results of this study are not representative of the general population of adults with TSC.

Another major limitation is the potential for misinterpreting open-ended responses to the questionnaire. For example, when asked about prenatal testing for a hypothetical future pregnancy, many individuals stated that they did not want to have a child with TSC. Due to the context of the question, this was interpreted as considering termination of the pregnancy if affected. However, the participants may have misinterpreted the question as asking if they would actively choose to have a future pregnancy, not that in this scenario the pregnancy had already happened. Since we were unable to ask follow-up questions for answers that were unclear, it is possible that our interpretation of the response was inaccurate.

Finally, since this was an anonymous online survey, it is possible that responses provided were not those of the individual diagnosed with TSC. In our survey, 29 individuals (16.57%) reported that they have intellectual disability. This result is somewhat surprising given that the questionnaire's language level and format would likely prove difficult for individuals with special needs. While it is possible that these individuals have a borderline diagnosis and were able to respond on their own or with some assistance, most likely these responses were provided by family members on the

individual's behalf. Therefore, the responses to this questionnaire may not reflect these individual's actual opinions and feelings.

Research Recommendations

This study was the first of its kind to investigate knowledge, disease burden, and reproductive decisions in adults with TSC. More research is needed to better understand the adult population. Most published studies focus on children diagnosed with TSC. Individuals who are diagnosed as children typically have more severe symptoms such as infantile spasms or intellectual disability which brings them to medical attention sooner. In order to better address concerns of mildly affected adults with TSC, we need more data on which symptoms these individuals experience and how these symptoms affect their daily lives. As demonstrated by our disease burden/quality of life instrument, TSC can have both physical and psychological impacts on even mildly affected adults. In order to better counsel adults with TSC, we need to know how TSC is impacting their lives. In particular, we need more studies investigating the impact of uterine tumors on the reproductive health of women with TSC.

Future studies should also investigate uptake of genetic testing in adults with TSC, and genetic testing results. In our study *TSC2* pathogenic mutations were only found in 38.24% of individuals who had genetic testing. This is significantly lower than the estimated 51-82% of individuals with *TSC2* pathogenic variants which is currently cited in the literature (Caban et al., 2017). While there is overlap in symptoms for *TSC1* and *TSC2* pathogenic variants, generally speaking, individuals with *TSC2* pathogenic variants have an earlier onset of seizures, lower cognitive scores, more skin lesions, and greater tumor

burden in the brain, kidneys, and liver (Caban et al., 2017). Therefore, it is possible that mildly affected adults with TSC are less likely to have a *TSC2* pathogenic variant than the general TSC population.

When it comes to reproductive decisions in adults with TSC, there were a few gaps in our study which should be addressed by future research. Future research should consider recruiting participants from a wider population such as at a TSC clinic or specialty care center where individuals are being treated for their symptoms of TSC. By recruiting from both support groups and clinic settings, study participants may be more representative of the general population of adults with TSC. Future studies should also consider using either more open-ended responses or an interview format to better understand the thought processes of participants. Finally, future studies should ask participants who were diagnosed with TSC in adulthood whether their reproductive decisions have changed over the course of their life.

Tables

Table 2.1 Summary of Participant Demographics

Category	Response	Participants (N)	Percentage (%)
Age	20 and Under	15	8.57
	21-25	29	16.57
	26-30	36	20.57
	31-35	31	17.71
	36-40	35	20.00
	41 and Over	29	16.57
	Total	175	100
Sex	Female	137	78.29
	Male	35	20.00
	Prefer Not to Answer	3	1.71
	Total	175	100
Relationship Status	Single, never married	57	33.14
	In a Serious Relationship or Engaged	38	22.09
	Married or in a Domestic Partnership	70	40.70
	Separated or Divorced	7	4.07
	Total	172	100
Highest Education Level Attained	Some High School	8	4.65
	High School Diploma or GED	30	17.44
	Some College	34	19.77
	Vocational, Technical, or Trade School	10	5.81
	Associate's Degree	17	9.88
	Bachelor's Degree	46	26.74
	Graduate or Professional Degree	27	15.70
	Total	172	100

Table 2.2 Participants' Current Family Structure

Fifty-three participants (30.29%) currently have children. Fifty-eight participants (33.14%) reported at least one affected family member. Percentages represent the number of participants who gave the specified response out of the total survey population (n = 175).

Category	Response	Participants (N)	Percentage (%)
Current Number of Children	None	122	69.71
	One	21	12.00
	Two	23	13.14
	Three	8	4.57
	Four	1	0.57
Family Members Diagnosed with TSC	Parent	34	19.43
	Sibling	15	8.57
	Child	30	17.14
	Other Family	23	13.14
	Any Family Member Affected	58	33.14

Table 2.3 Summary of Participant's and Family Member's Symptoms

Percentages represent the number of participants who reported the specified symptom for themselves out of the total who reported symptoms (n = 175) or the specified symptom for affected family member(s) out of the total who reported symptoms for family members (n = 52).

Symptom	Affected Individual	Individuals (N)	Percentage (%)
Angiofibromas	Self	142	81.14
	Family Member	22	42.31
Angiomyolipomas	Self	123	70.29
	Family Member	22	42.31
Ash-Leaf Spots	Self	132	75.43
	Family Member	35	67.31
Autism	Self	19	10.86
	Family Member	16	30.77
Cardiac Rhabdomyomas	Self	39	22.29
	Family Member	18	34.62
Cortical Tubers	Self	102	58.29
	Family Member	31	59.62
Developmental Delay	Self	38	21.71
	Family Member	25	48.08
Forehead Plaques	Self	75	42.86
	Family Member	4	7.69
Intellectual Disability	Self	29	16.57
	Family Member	23	44.23
Learning Disability	Self	71	40.57
	Family Member	28	53.85
Lymphangioleiomyomatosis	Self	40	22.86
	Family Member	7	13.46
Periungual Fibromas	Self	89	50.86
	Family Member	20	38.46
Seizures	Self	89	50.86
	Family Member	36	69.23
Shagreen Patches	Self	89	50.86
	Family Member	23	44.23
Subependymal Nodules	Self	51	29.14
	Family Member	18	34.62
Other Symptom(s)	Self	31	17.71
	Family Member	9	17.31

Table 2.4 Disease Burden/Quality of Life Average Score by Question

Participants were asked how often they agree with the statement listed on a five point scale of "never" to "very often." Negative statements were scored 1 for "never" to 5 for "very often." Positive statements (*) were scored in reverse.

Statement	Average	Median
I feel like I am in control of my life. *	2.44	2
I think about my TSC.	3.78	4
I tend to stay home because of my symptoms.	2.35	2
My symptoms limit the things I can do.	2.61	3
I worry about my appearance.	2.80	3
I have trouble sleeping.	3.21	3
I feel comfortable meeting new people. *	2.77	3
I feel good about my social life. *	2.84	3
I feel different from those around me.	3.35	3
I had trouble in school.	2.98	3
I feel like I have the support I need. *	2.40	2
I am frustrated by my symptoms.	3.26	3
I experience pain because of my TSC.	2.57	3
My symptoms make me anxious.	3.12	3

Table 2.5 Summary Table of Regression Models of the Effect of Various Factors on Participants' Desired Number of Children

None of the factors investigated had a statistically significant effect on the participants' desired number of children.

Variable	F	df	p	R^2
Knowledge Score	0.421	(1, 93)	.518	.005
Symptom Severity Score	2.566	(1, 97)	.112	.026
Facial Symptom Severity Score	0.872	(1, 101)	.353	.009
Seizures in Participant	0.001	(1, 101)	.978	.000
Disease Burden/Quality of Life Score	0.884	(1, 97)	.350	.009
Symptom Severity in Family	0.442	(1, 101)	.507	.004
Family History of Autism	0.052	(1, 101)	.820	.001
Family History of Intellectual Disability	0.166	(1, 101)	.684	.002

Table 2.6 Summary Table of Regression Models of the Effect of Various Factors on Participants' Choice of Reproductive Method

None of the factors investigated had a statistically significant effect on the participants' choice of traditional conception, adoption, use of donor gametes or embryos, or preimplantation genetic diagnosis.

Variable	Reproductive Method	F	df	p	R^2
Symptom Severity Score	Traditional	0.152	(1, 98)	.697	.002
	Adoption	0.005	(1, 98)	.946	.000
	Donor	0.161	(1, 98)	.689	.002
	PGD	0.365	(1, 98)	.547	.004
Disease Burden/Quality of Life Score	Traditional	0.232	(1, 96)	.631	.002
	Adoption	2.384	(1, 96)	.126	.024
	Donor	0.054	(1, 96)	.816	.001
	PGD	1.460	(1, 96)	.230	.015
Symptom Severity in Family	Traditional	0.034	(1, 98)	.855	.000
	Adoption	0.827	(1, 98)	.365	.008
	Donor	0.003	(1, 98)	.956	.000
	PGD	0.635	(1, 98)	.427	.006

Table 2.7 Themes Identified as Factors for Choice of Reproductive Method

Eighty-nine individuals provided an open-ended response for what factors influenced which reproductive method they were considering. Thematic analysis revealed eight major themes. Some statements could be coded into multiple themes. Statements which did not fit into a theme were classified as "other."

Theme	Example Response	Participants (N)	Percentage (%)
Personal Health or Medical Advice	"Pregnancy would be dangerous for me with my renal AMLs, and wouldn't help my odds of developing LAM (which I do not have yet, but some research links it and estrogen levels)."	23	25.84
Desire to Not Pass on TSC to a Child	"I don't want to risk my children inheriting TSC. I knew I wanted to do PGD at age 21 when I first found out that it was possible."	33	37.08
Financial Concerns	"I would like tradition [sic], because money is a huge factor in this. I have looked up PGD and it seems expensive."	9	10.11
Desire for Biological Children	"I've always wanted to be a mom and although I'm not opposed to adoption and would love them just as much, I would prefer to have my own kids."	17	19.10
Thoughts/Desires of Partner	"My partners will [sic] to take the risk."	9	10.11
Ethical Concerns	"I don't like the idea of discarding unhealthy eggs which have be [sic] fertilized in the PGD process."	2	2.25
Not Technologically Possible	"PGD not available because I have NMI."	6	6.74
Fertility Issues	"I had a hysterectomy almost 2 years ago. I had a Pecoma."	9	10.11
Other	"I have a sister who is adopted and I have tremendous anxiety about putting my body through pregnancy."	23	25.84

Table 2.8 Themes Identified as Factors for Decisions About Prenatal Testing

A total of 142 individuals provided an open-ended response for what factors influenced whether they would undergo prenatal testing for TSC in a hypothetical future pregnancy. Thematic analysis revealed eight major themes. Some statements could be coded into multiple themes. Statements which did not fit into a theme were classified as "other."

Theme	Example Response	Participants (N)	Percentage (%)
Possibly Considering Termination	"TSC is a terrible chronic disease. I do not want to be responsible for knowingly bringing a child(ren) into this world who is affected by this condition. Mild case or severe case. Does not matter to me."	30	21.13
Ethical Concern/ Against Termination	"I don't believe in abortion and would love the child regardless of the TSC."	4	2.82
Being Informed/ Prepared	"I would want to be prepared, including finding a medical team, if my child were to be diagnosed with TSC. I would also want to be able to prepare my life and home for the possibility of a child with severe delays."	67	47.18
Previous Experience	"I have already done that, and ended a pregnancy because the tests showed TSC2."	4	2.82
Risk of Test	"Amnio has risks, and may not yield a result anyway since I don't know my mutation."	4	2.82
Financial Concern	"genetic testing is expensive"	4	2.82
Not Technologically Possible	"I did not test positive for the gene. I was clinically diagnosed based on multiple issues."	4	2.82
Accepting of Whatever Happens	"The results wouldn't change my happiness."	12	8.45
Other	"I would consider testing after the baby were [sic] born."	25	17.61

Figures

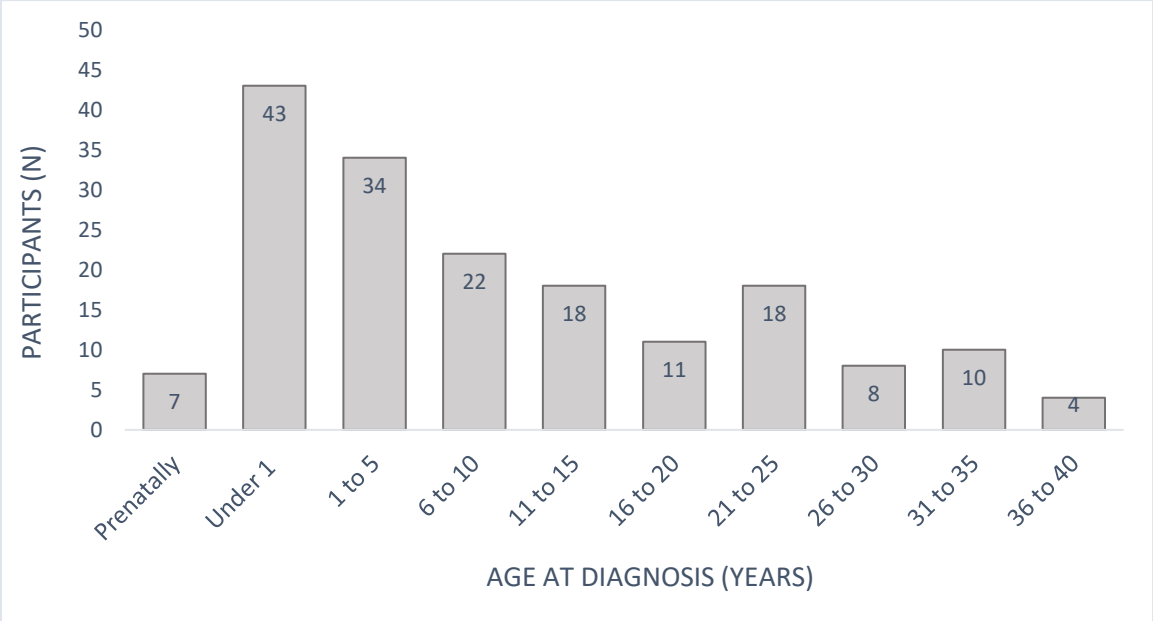

Figure 2.1 Participants' Age at Diagnosis of TSC
Participants (n = 175) were asked if they were diagnosed prenatally, under one year of age, or over one year of age. Those diagnosed over one year were asked to provide age in years. The median age at diagnosis was 7 years.

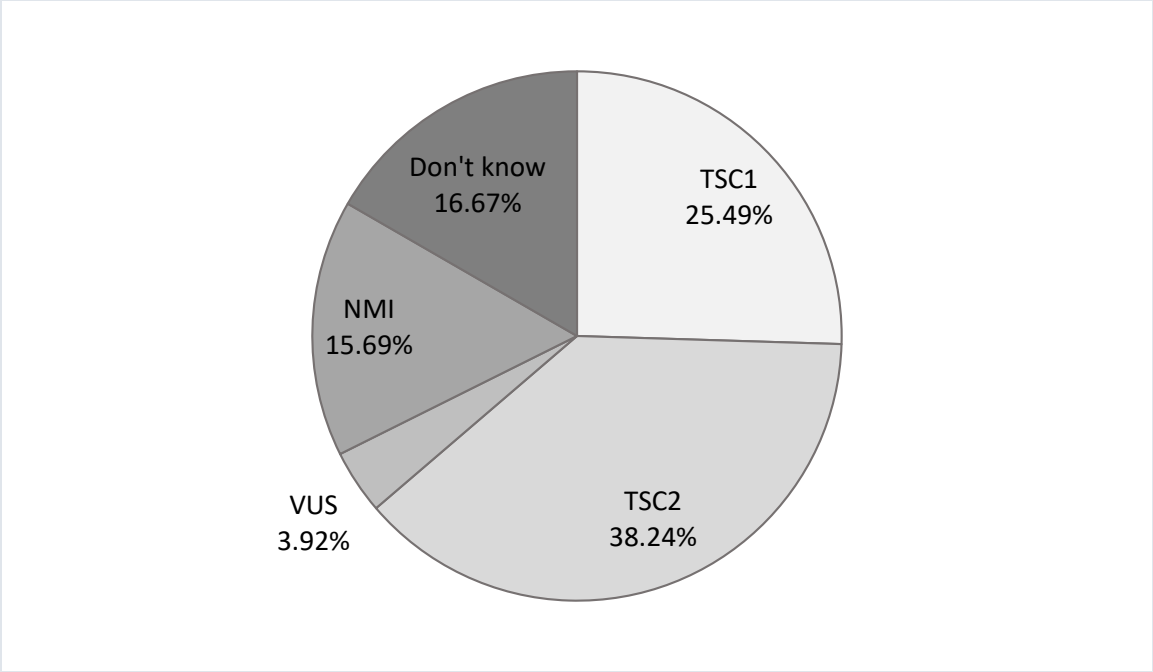

Figure 2.2 Genetic Testing Result of Participants

A total of 102 participants reported having genetic testing. Participants reported that their genetic test found either a pathogenic mutation in *TSC1* (n = 26) or *TSC2* (n = 39), a Variant of Uncertain Significance (VUS) (n = 4), or No Mutation Identified (NMI) (n = 16). A total of 17 participants were unable to remember their testing result.

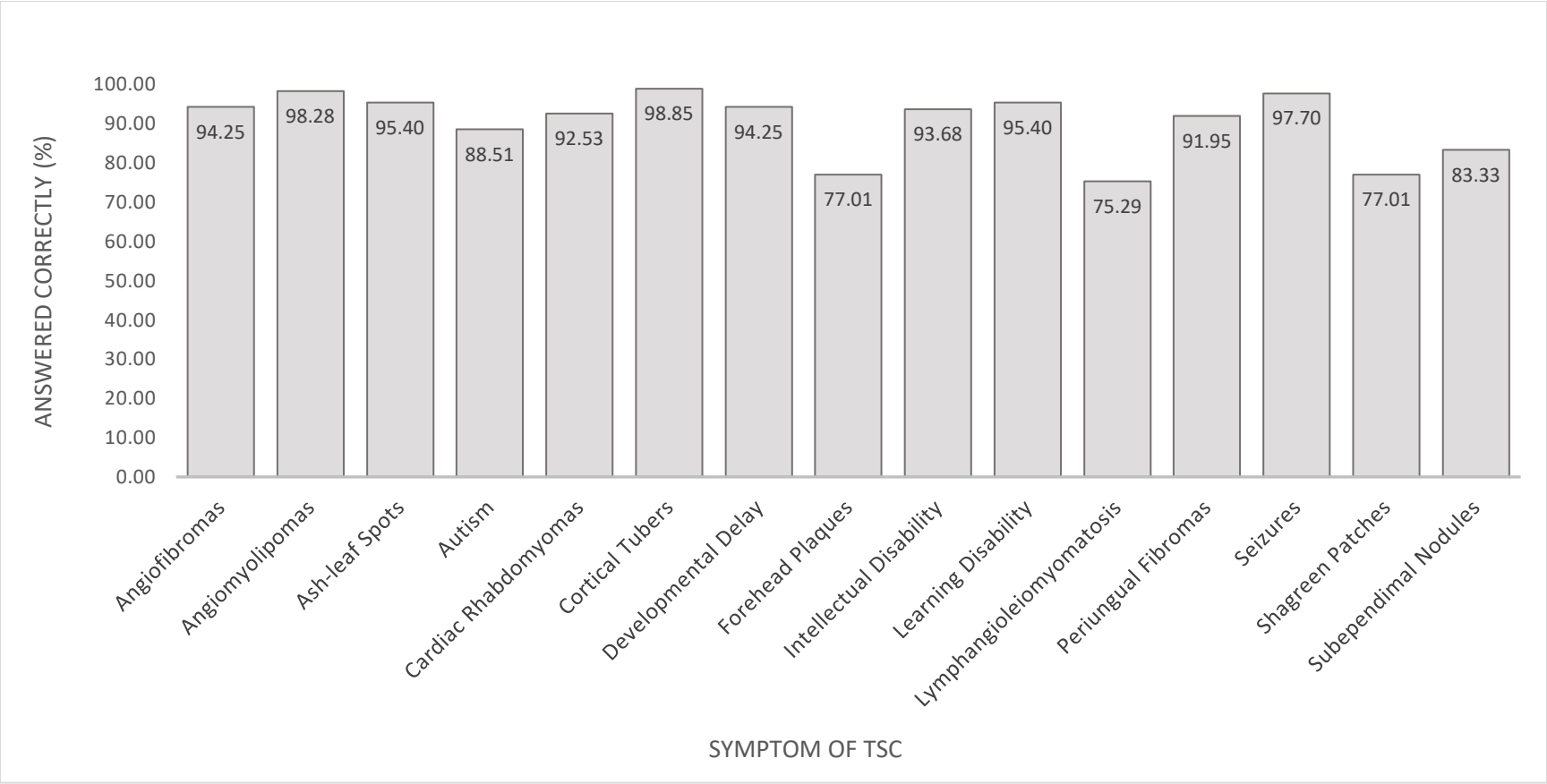

Figure 2.3 Results of the TSC-Associated Symptoms Quiz

The percent of participants who correctly identified the listed symptom is based on the total number of participants who provided at least one answer to this question (n = 174). Some participants did not provide an answer for each symptom.

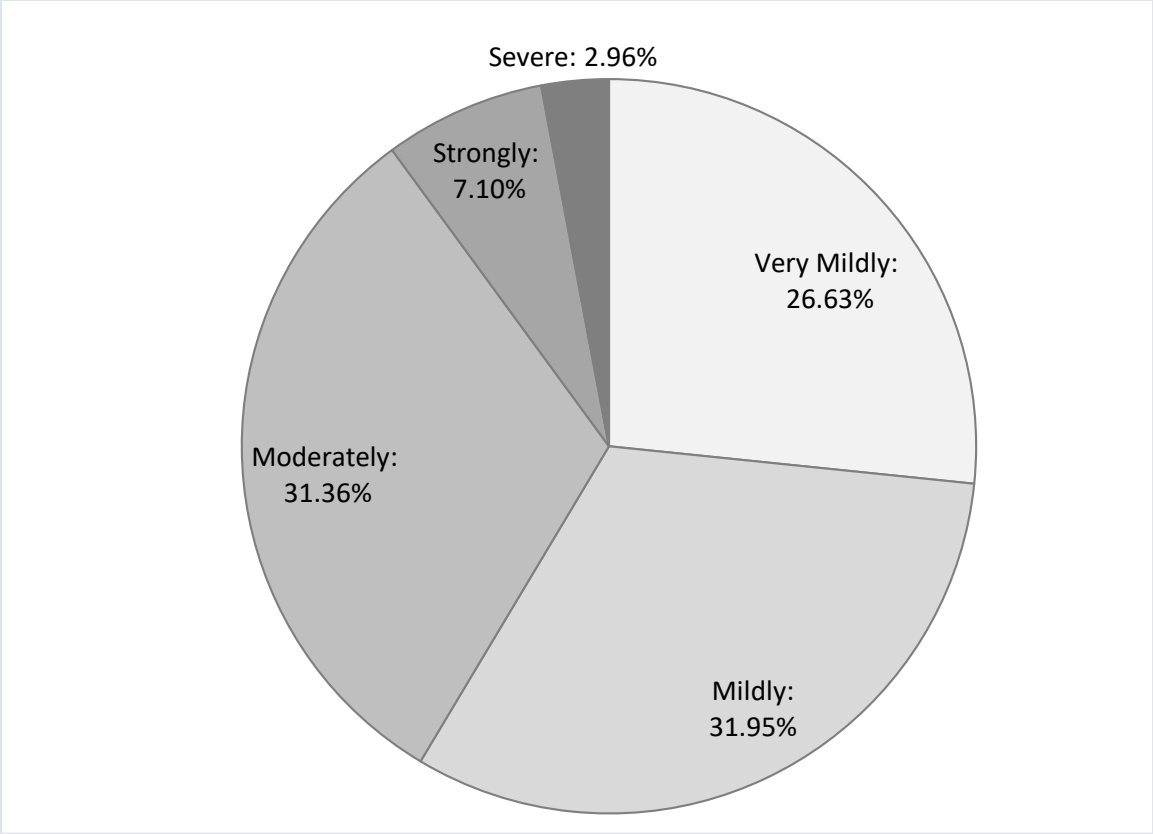

Figure 2.4 Participants' Perceived Symptom Severity
Participants were asked to rate their symptom severity on a five point scale of "very mildly" to "severely" affected. A total of 169 participants provided a response: very mildly (n = 45), mildly (n = 54), moderately (n = 53), strongly (n =12), and severely (n = 5).

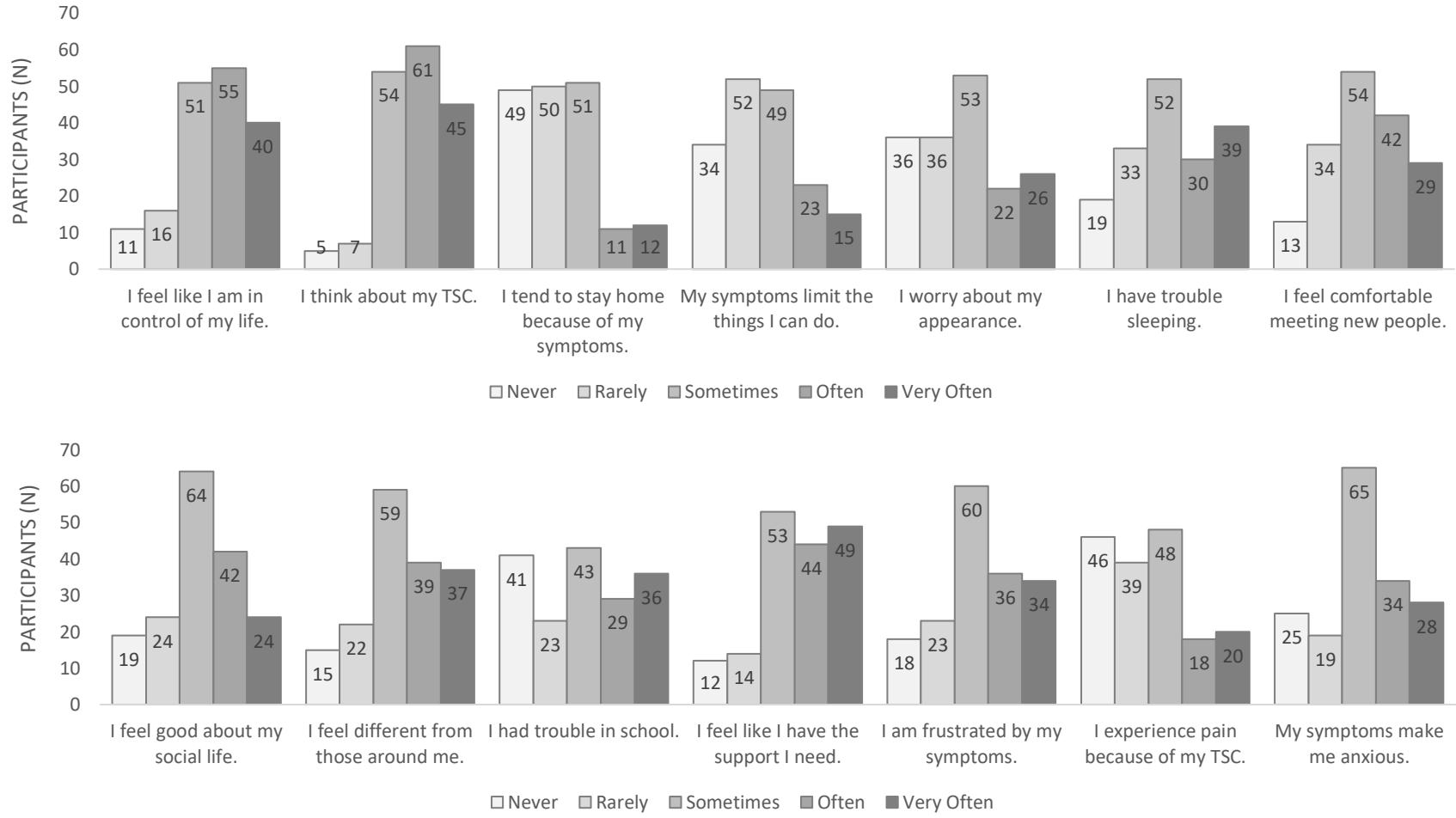

Figure 2.5 Perceived Impact of TSC on Participants' Lives

Participants were asked how often they agreed with the statement on a five point scale ranging from "never" to "very often." The number of participants who agreed with each option is indicated at the end of each bar.

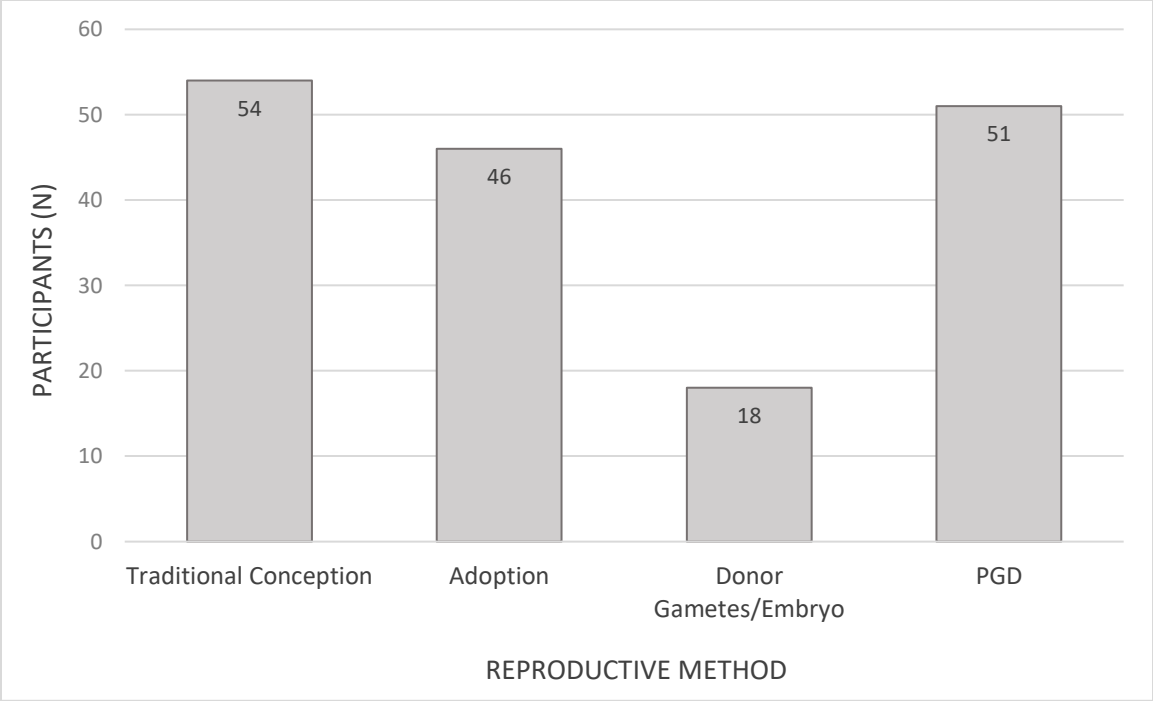

Figure 2.6 Reproductive Methods Being Considered

Bars represent the number of participants considering traditional conception, adoption, using donor gametes or embryos, and/or preimplantation genetic diagnosis (PGD). Participants were able to select more than one response. A total of 102 participants provided a response.

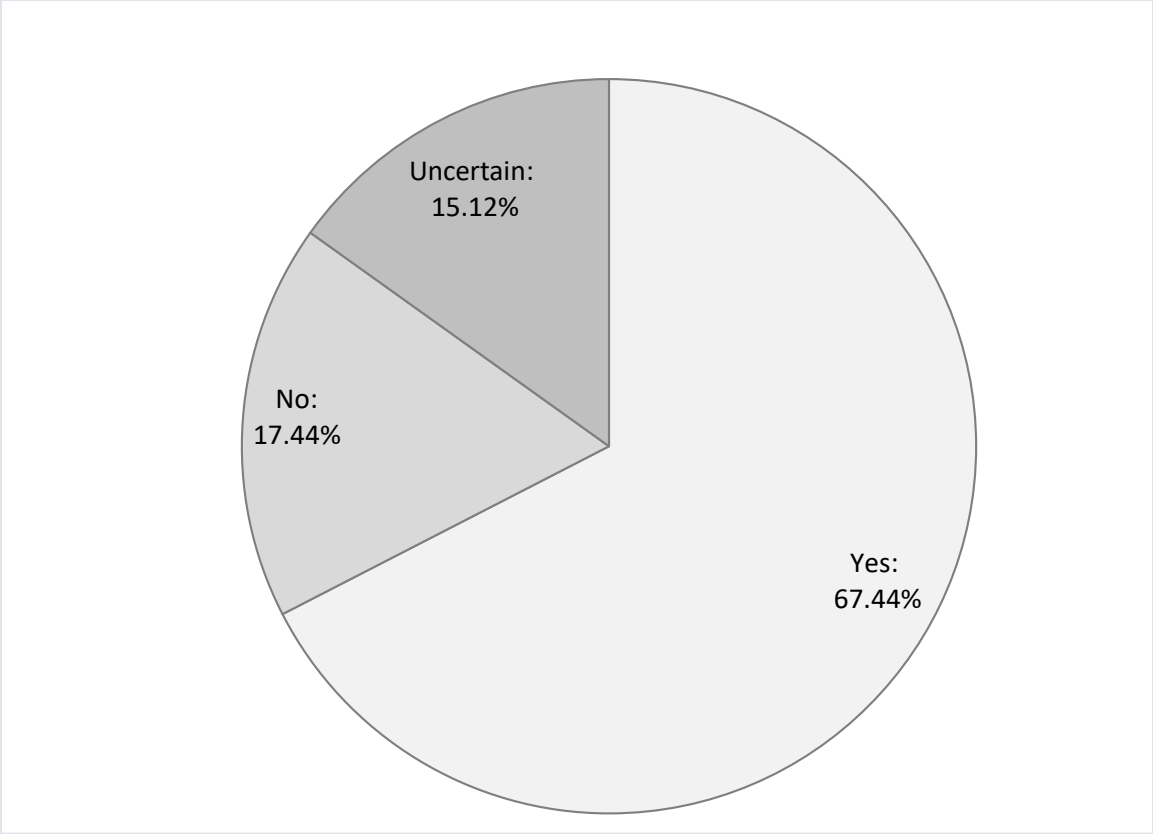

Figure 2.7 Participants' Interest in Prenatal Testing for TSC
Participants were asked whether they would consider prenatal testing of a hypothetical future pregnancy. Out of 172 responses, 116 said yes, 30 said no, and 26 were uncertain.

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Appendix A

Recruitment Flyer:

Are you an adult aged 18-45 diagnosed with tuberous sclerosis complex (TSC)?

We would like to hear from you!

While a lot of research has been done on the medical aspects of tuberous sclerosis complex (TSC), not much has been done on how TSC affects people's lives. I would like to change that. I am a genetic counseling student at the University of South Carolina. From July-December 2018 I will be conducting an anonymous online survey to better understand how TSC affects adults aged 18-45 in their daily lives including family planning. This survey is completely voluntary. It will include questions about the following topics:

- *basic demographics (age, sex, education level, etc.)*
- *symptoms that occur in TSC*
- *symptoms that you and your affected family members experience*
- *how TSC affects your daily life*
- *how TSC affects your family planning*

The survey takes about 8-10 minutes to complete. Participants have the opportunity to enter a drawing for a $25 Amazon e-gift card. The drawing will be conducted once the survey period has ended in December 2018. To enter the drawing participants will need to provide an email or cellphone number, however the survey can be taken without providing contact information. Your contact information will not be shared or used for any other purpose than to notify you if you win the drawing.

To participate in the survey, please go to the following website:

https://www.surveymonkey.com/r/Adults_with_TSC

If your smart phone or tablet has a QR Reader you can use this link:

If you have any questions about the survey, please contact Diane Biederman at Diane.Biederman@uscmed.sc.edu

Appendix B

SurveyMonkey.com Anonymous Online Survey:

Welcome to the Adults with TSC Survey!

Thank you for your interest in our survey! We are conducting this survey in order to better understand how adults are affected by tuberous sclerosis complex (TSC) in their daily lives including family planning. This survey is anonymous and completely voluntary. You may choose to stop at any time or skip any questions that you do not wish to answer (except questions 1 and 2 which are required to meet survey participation requirements). To participate, you should be an adult aged 18-45 who has been diagnosed with TSC. This survey is intended to get the opinions of people who have TSC themselves. While parental or spousal opinions can be important factors, we ultimately want your opinion so please answer for yourself.

The survey is divided into 5 sections:

1) ***Demographics:*** **basic questions about you such as age, sex, education level, etc.**
2) ***Family Planning:*** **questions about your plans for children**
3) ***Features of TSC:*** **includes general questions about TSC and symptoms experienced by you or your family members**
4) ***Your experience with TSC:*** **questions about how TSC affects your daily life**
5) ***Closing Statement:*** **how did you hear of the survey and entry into Amazon e-gift card drawing**

It will take about 10 minutes to complete the survey. At the end of the survey, you will have the opportunity to enter a drawing for a $25 Amazon e-gift card. Entry into the drawing will require either an email or mobile phone number to be provided for delivery purposes. Your contact information will not be used for any other reason or shared with any other parties. You do not have to provide your contact information to complete the survey, however without contact information, you will not be entered into the drawing.

This survey is being conducted as part of a research thesis for Diane Biederman, a genetic counseling student at the University of South Carolina. If you have any questions or concerns about the survey before you begin, please email Diane at Diane.Biederman@uscmed.sc.edu.

By clicking "next" you are agreeing to participate in this survey.

Survey Eligibility

Please answer the following questions to determine if you meet the survey requirements.

* 1. Have you been diagnosed with tuberous sclerosis complex (TSC)?

- ◯ Yes
- ◯ No

* 2. Are you between the ages of 18-45?

- ◯ Yes
- ◯ No

Part 1: Demographics

3. What is your current age?

4. Are you biologically male or female?

- ◯ Male
- ◯ Female
- ◯ Prefer not to answer

5. Are you in a relationship?

- ◯ Single, never married
- ◯ In a serious relationship or engaged
- ◯ Married or in a domestic partnership
- ◯ Separated or Divorced
- ◯ Widowed

6. What is your highest level of education?

- ◯ Some high school
- ◯ High school diploma or GED
- ◯ Some college
- ◯ Vocational, technical, or trade school
- ◯ Associate's degree
- ◯ Bachelor's degree
- ◯ Graduate or professional degree

7. When were you diagnosed with TSC?

If you are not sure, please give your best guess.

- [ ] Prenatally (before I was born)
- [ ] Under 1 year of age
- [ ] Over 1 year of age (please specify age in years)

8. Has anyone else in your family been diagnosed with TSC?

Please enter the number of individuals in each category who have been diagnosed with TSC. If you do not have family members with TSC, please leave blank.

Parent	
Child	
Sister or Brother	
Other family members	

9. Have you had genetic testing for your TSC?

(A DNA test to identify the cause of your TSC)

- ◯ Yes
- ◯ No
- ◯ I don't know

Part 1: Demographics

10. What was the result of your genetic test?

- ◯ I have a pathogenic (disease-causing) change in *TSC1*.
- ◯ I have a pathogenic (disease-causing) change in *TSC2*.
- ◯ They found a change, but are not sure if it caused my TSC. (This may have been called a "variant of uncertain significance" or "VUS" by your doctor.)
- ◯ The test didn't find any changes in my *TSC1* or *TSC2* genes.
- ◯ I don't know/remember my result.

Part 2: Family Planning

The following questions are about your plans for your current or future family.

11. How many children do you currently have?

12. Would you like to have (or have more) children in the future?
(may be biological or not biological)

- ◯ Yes
- ◯ No
- ◯ Undecided

13. When thinking about your future family, how many children would you like to have in total?
Please enter the number in the space provided. If "undecided", please enter your "maybe" number.

14. Which of the following reproductive options are you considering?

Select all that apply.

- ☐ *Traditional conception*
- ☐ *Adopted children*
- ☐ *Using donor eggs, sperm, or embryos (having a pregnancy that is not biologically related to you)*
- ☐ *Preimplantation genetic diagnosis (PGD)*

PGD is a procedure that uses IVF to create embryos which are then tested for a genetic condition that runs in the family. Typically, the embryos which do not have the condition will be selected for implantation. This procedure lets families have biological children who will not have the genetic condition.

15. What factors determined your answer to question 14?

The following questions are hypothetical. What would you do in the following situations?

16. If you did not have TSC, would the number of children you would like to have be different?

- ○ Yes
- ○ No
- ○ Uncertain/Maybe

17. How many children would you like to have in total if you did not have TSC?

18. If you or your partner were to become pregnant, would you consider testing your baby for TSC before he or she is born?

Prenatal testing (testing before birth) would involve collecting a sample of the baby's DNA by amniocentesis (collection of amniotic fluid from the womb) or chorionic villus sampling (collecting a sample of the placenta), growing the sample in a lab, and then testing the baby's DNA for a known change to the *TSC1* or *TSC2* genes.

◯ Yes

◯ No

◯ Uncertain

19. What factors determined your answer to question 18?

Part 3: Features of TSC

The following questions are intended to measure how familiar people diagnosed with TSC are with features of the condition. Please answer based on your current understanding of symptoms of TSC. Please do not look up symptoms. If you are not sure, please give your best guess. While medical terminology will be used, a short description will be provided for each condition.

Please note: the symptoms listed below may or may not be associated with TSC. The list also may not include all symptoms associated with TSC. If you have any questions or concerns about potential symptoms of TSC, please contact your healthcare provider, a genetic counselor, or a TSC clinic.

To find a genetic counselor, click here.
To find a TSC clinic, click here.

20. Which of these symptoms can be caused by TSC?

	Yes, TSC can cause this symptom.	No, this symptom is not associated with TSC.
Angiofibroma: red, pink, or skin colored bumps on the face, particularly located around the edge of the nose or in a butterfly shape on the nose, cheeks, and forehead	○	○
Angiomyolipoma: benign (noncancerous) tumors in the kidney	○	○
" *Ash-leaf spot* or *hypomelanotic macule:* oval or leaf-shaped areas of skin that is lighter than the surrounding skin	○	○
Arthritis: pain, swelling, and stiffness of the joints caused by the lining of joints breaking down	○	○
Autism: condition characterized by difficulty with social interactions, communication, and repetitive behaviors	○	○
Cardiac rhabdomyoma: benign (noncancerous) heart tumor	○	○

	Yes, TSC can cause this symptom.	No, this symptom is not associated with TSC.
Chronic obstructive pulmonary disease (COPD) lung disease caused by inflammation (swelling of tissue) resulting in a cough with heavy mucus, wheezing, shortness of breath, and chest tightness	○	○
Cortical tubers: benign (noncancerous) tumors in the cortex (outer layers) of the brain	○	○
Cleft lip: a split in the upper lip that is present at birth	○	○
Developmental delay: not meeting milestones like walking or talking within the typical timeframe	○	○
Eczema: dry, itchy skin which may be red to brownish-gray and may have small raised bumps which can leak fluid when scratched	○	○
Forehead plaques or cephalic plaques: smooth patches of raised skin on the forehead, scalp, or face which may be red or flesh colored	○	○
Glioma: malignant (cancerous) tumor of the brain	○	○
Hearing loss: partial or complete loss in the ability to hear	○	○
Intellectual disability: historically called “mental retardation”; when an individual has problems learning or understanding things making it difficult to live an independent life	○	○

Learning difficulty: when an individual has problems in school with skills like reading or math, but is still able to live a typical independent life	○	○
Lymphangioleiomyomatosis (LAM): overgrowth of smooth muscle in the lungs and the formation of cysts (fluid filled spaces) that block airflow leading to breathing difficulty	○	○
Periungual fibromas: growths around the nails on the fingers or toes	○	○
Polydactyly: extra fingers or toes	○	○
Port-wine stain: dark red or purplish-red mark on the skin that looks like spilled wine	○	○
Seizures: sudden, uncontrolled electrical signals in the brain that causes changes in behavior, movements, feelings, or levels of consciousness	○	○
Shagreen patches: raised skin with the texture of an orange peel, usually on the lower back	○	○
Stroke: when a blood vessel carrying blood to the brain becomes blocked or bursts resulting in loss of blood flow and damage to the brain	○	○
Subependymal nodules (SEN): Benign (noncancerous) tumors growing in the walls around the ventricles (fluid-filled spaces) in the brain	○	○

21. If you were to have a biological child with a partner who does not have TSC, what is the chance your child would have TSC?

- ◯ 0% or "I can't have a child with TSC."
- ◯ 25% or "1 in 4 chance"
- ◯ 50% or "1 in 2 chance"
- ◯ 75% or "3 in 4 chance"
- ◯ 100% or "I am guaranteed to have a child with TSC."

The next questions are about symptoms of TSC you or your family members experience. The symptoms listed are the same as in question 20 and may or may not be associated with TSC. The list may not include all symptoms of TSC.

22. What symptoms of TSC do you and your family members experience?

Select all that apply. If you are unsure about a symptom, please leave the option blank.

	I have this symptom.	One or more family members have this symptom.
Angiofibroma: red, pink, or skin colored bumps on the face, particularly located around the edge of the nose or in a butterfly shape on the nose, cheeks, and forehead	☐	☐
Angiomyolipoma: benign (noncancerous) tumors in the kidney	☐	☐
"Ash-leaf spot" or hypomelanotic macule: oval or leaf-shaped areas of skin that is lighter than the surrounding skin	☐	☐
Arthritis: pain, swelling, and stiffness of the joints caused by the lining of joints breaking down	☐	☐
Autism: condition characterized by difficulty with social interactions, communication, and repetitive behaviors	☐	☐
Cardiac rhabdomyoma: benign (noncancerous) heart tumor	☐	☐

Chronic obstructive pulmonary disease (COPD) lung disease caused by inflammation (swelling of tissue) resulting in a cough with heavy mucus, wheezing, shortness of breath, and chest tightness	☐	☐
Cortical tubers: benign (noncancerous) tumors in the cortex (outer layers) of the brain	☐	☐
Cleft lip: a split in the upper lip that is present at birth	☐	☐
Developmental delay: not meeting milestones like walking or talking within the typical timeframe	☐	☐
Eczema: dry, itchy skin which may be red to brownish-gray and may have small raised bumps which can leak fluid when scratched	☐	☐
Forehead plaques or cephalic plaques: smooth patches of raised skin on the forehead, scalp, or face which may be red or flesh colored	☐	☐
Glioma: malignant (cancerous) tumor of the brain	☐	☐
Hearing loss: partial or complete loss in the ability to hear	☐	☐
Intellectual disability: historically called “mental retardation”; when an individual has problems learning or understanding things making it difficult to live an independent life	☐	☐
Learning difficulty: when an individual has problems In school with skills like reading or math, but is still able to live a typical independent life	☐	☐

Lymphangioleiomyomatosis (LAM) overgrowth of smooth muscle in the lungs leading to blockage of airflow and shortness of breath, fluid can also collect in pockets of the lung	☐	☐
Periungual fibromas: growths around the nails on the fingers or toes	☐	☐
Polydactyly: extra fingers or toes	☐	☐
Port-wine stain: dark red or purplish-red mark on the skin that looks like spilled wine	☐	☐
Seizures: sudden, uncontrolled electrical signals in the brain that causes changes in behavior, movements, feelings, or levels of consciousness	☐	☐
Shagreen patches: raised skin with the texture of an orange peel, usually on the lower back	☐	☐
Stroke: when a blood vessel carrying blood to the brain becomes blocked or bursts resulting in loss of blood flow and damage to the brain	☐	☐
Subependymal Nodules (SEN): Benign (noncancerous) tumors growing in the walls around the ventricles (fluid filled spaces) in the brain	☐	☐
Other symptoms not listed: Please list below.	☐	☐

Other (please note if the symptom is yours, a family member's, or both)

Part 4: Your experience with TSC

The following questions are about how TSC affects your daily life.

23. How would you characterize your own symptoms of TSC?

- ◯ Very mildly affected
- ◯ Mildly affected
- ◯ Moderately affected
- ◯ Strongly affected
- ◯ Severely affected

24. Thinking about your experience with TSC, how often would you agree with the following statements?

	Never	Rarely	Sometimes	Often	Very often
I feel like I am in control of my life.	◯	◯	◯	◯	◯
I think about my TSC.	◯	◯	◯	◯	◯
I tend to stay home because of my symptoms.	◯	◯	◯	◯	◯
My symptoms limit the things I can do.	◯	◯	◯	◯	◯
I worry about my appearance.	◯	◯	◯	◯	◯
I have trouble sleeping.	◯	◯	◯	◯	◯
I feel comfortable meeting new people.	◯	◯	◯	◯	◯
I feel good about my social life.	◯	◯	◯	◯	◯
I feel different from those around me.	◯	◯	◯	◯	◯
I had trouble in school.	◯	◯	◯	◯	◯
I feel like I have the support I need.	◯	◯	◯	◯	◯
I am frustrated by my symptoms.	◯	◯	◯	◯	◯
I experience pain because of my TSC.	◯	◯	◯	◯	◯
My symptoms make me anxious.	◯	◯	◯	◯	◯

Part 5: Closing Statement

Thank you for completing this survey! Your time and responses are greatly appreciated and will help us better understand the adult TSC population. Before you go...

25. How did you hear about this survey?

- ◯ A flyer at the 2018 World TSC Conference
- ◯ Through an online support group/online newsletter.
- ◯ A flyer at a TSC clinic
- ◯ Through a friend

26. Would you be open to a possible follow-up interview?

If yes, please make sure to enter your contact information (mobile phone or email) in the Amazon e-gift card drawing.
If no, still enter the drawing. We promise not to contact you unless you win.

- ☐ Yes
- ☐ No

27. If you would like to enter the $25 Amazon e-gift card drawing, please provide an email or mobile phone number where we can send your prize.

Your contact information will not be used for any purpose other than the drawing or to contact you if you agreed to a follow-up interview. Your information will not be shared with any other parties. If you are concerned that your email may reveal your identity, please provide a mobile phone number instead.